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Female	114.7	116.4	117.7	118.7	120.4	123.6	127.1	129.8	132.5	133.7	135.4
DIASTOLIC **Male	76.4	78.1	78.8	79.5	80.4	81.4	82.3	83.3	84.3	84.5	84.0
Female	75.8	77.1	78.0	78.6	79.9	81.9	83.9	85.4	86.8	86.8	84.4

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*Blood Pressure, Report of Joint Committee on Mortality of The Association of Life Insurance Medical Directors and The Actuarial Society of America. New York, 1925. pp. 10, 52.

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

APRIL, 1948

ORIGINAL ARTICLES

HISTOPLASMOSIS AND TORULOSIS AS CAUSES OF ADRENAL INSUFFICIENCY

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Since the time of Thomas Addison it has been recognized that tuberculosis is the most frequent cause of the syndrome of adrenal insufficiency due to massive destruction of the glands. It is well known, however, that other microörganisms as well as neoplasms may destroy enough adrenal tissue to produce the signs and symptoms of adrenal insufficiency. It is our purpose in the present communication to point out the less well known fact that certain fungus diseases, by means of massive destruction of the adrenal glands, may likewise produce the syndrome of insufficiency of adrenal hormones. It is felt that despite their relative infrequency, histoplasmosis and torulosis should be kept in mind in any differential diagnosis of the syndrome. We have therefore reviewed all cases of adrenal involvement by histoplasmosis and by torulosis available to us, and present an analysis of the data in Tables 1 and 2.

In Table 1, it will be noted that a total of 19 cases (including Case 1 herein reported) of involvement of the adrenal glands by *Histoplasma capsulatum* have been reported. Of these, 12 have shown some degree of destruction of adrenal parenchyma, and in 9 there was massive destruction of such magnitude that death was presumably due to adrenal insufficiency. In Table 2 it will be noted that some symptoms of adrenal insufficiency

Table 1.—Summary of Reported Lesions of the Adrenal Glands Caused by Histoplasma Capsulatum and by Cryptococcus Neoformans (Torula Histolytica) (Including Present Cases)

Type of lesion	Number of cases: Histoplasmosis	Torulosis
Presence of organisms with or without foci of inflammatory cells	4[1,10,17,20]	5[4,6,24]
Partial necrosis without symptoms of adrenal insufficiency	4[2,9,12,21]	1[18]
Massive necrosis with adrenal insufficiency (including present cases)	9[15,16,17,22,23,25]	1
Not stated	2[3,7]	1[13]
Totals	19	8
Per cent of described lesions showing caseation	76%	28%

TABLE 2.—ANALYSIS OF CASES OF ADRENAL INSUFFICIENCY CAUSED BY HISTOPLASMA CAPSULATUM

Case reported by	Age	Sex	Race	Symptoms suggestive of adrenal insufficiency	Adrenal weight (gm.)	Description of adrenals
1. Parsons and Zarafonetis[17] (Case 24), 1938*	63	M	W	Weight loss, dehydration	50 60	Almost complete caseation necrosis surrounded by granulation tissue. Yeast present.
2. Parsons and Zarafonetis[17] (Case 53), 1940	49	M	W	Anorexia, severe weakness, B.P. 88/62, wt. loss	70 65	Firm gray tissue mixed with yellow areas of necrosis. No adrenal tissue seen.
3. Manchester, 1941 (quoted by Parsons and Zarafonetis[17])	63	M	W	"Evidence of adrenal insufficiency"	Not stated	Bilateral adrenal necrosis. Organisms in adrenals only.
4. Palmer, Amolsch and Shaffer,[16] 1942	45	M	W	Weakness, emaciation, B.P. 95/55	Not stated. Size 7 x 3.5 x 1 cm.	Rubbery, caseous many tubercles and pseudo-tubercles.
5. Van Pernis, Benson and Holinger,[23] 1943	63	M	W	Marked weakness, 80 lb. wt. loss, bronzing of skin	14.2 14.5	Thick fibrous capsules surround yellow-gray caseous tissue containing many yeasts.
6. Thomas and Morehead,[22] 1943*	44	M	W	Marked weakness, severe respiratory infection, B.P. 80/64. Weak pulse	36 52	Almost entirely replaced by light gray fibro-caseous material
7. Martin and Silber,[15] 1944	39	F	W	Marked weakness, wt. loss of over 45 lbs., gradual fall in B.P. from 194/110 to 100/60	Not stated. Rt. twice normal size. Left 10 x 5 x 4 cm.	Entire left gland replaced by firm nodular white tissue with caseous center. Right gland contained numerous nodules.
8. Ziegler,[25] 1946	58	F	W	Severe weakness, 70 lb. wt. loss, anorexia	Not stated. Size: 9 x 5 x 3 cm., and 7 x 4 x 2 cm.	Grayish yellow tissue with hemorrhage and necrosis. Only slight cortical remnants.
9. Rawson, Collins and Grant (Case 1), 1947	62	F	W	Marked weakness, wt. loss, fall in B.P.	60 65	Both glands replaced by caseous material surrounded by fibrous tissue.

* Co-existing pulmonary tuberculosis.

such as marked weakness, anorexia, dehydration, weight loss, low blood pressure, and bronzing of the skin were present in each case where massive adrenal destruction was found at autopsy. For the most part the importance of these symptoms was masked by other complaints referable to the involvement of other organs. It will further be noted that the appearance of the adrenal gland at autopsy was rather uniform. There was marked enlargement, and almost complete parenchymal replacement by yellowish-gray fibrocaseous tissue containing the causative organism.

Involvement of the adrenals by *Cryptococcus neoformans* (*Torula histolytica*) has been noted far less frequently. In Table 1 it is seen that only 8 such cases have been reported. Only 2 of these showed any necrosis, and in only 1 (Case 2 herein reported) was there necrosis extensive enough to produce the syndrome of adrenal insufficiency. Case reports of adrenal insufficiency caused by histoplasmosis and by torulosis, respectively, follow:

Case Reports. CASE 1. Mrs. A. K., a 62 year old white female, had always enjoyed excellent health until 2 months earlier when, for no apparent reason, she developed a small ulcer on the left ventral anterolateral aspect of her tongue. The lesion was quite painful from the start. Smears for Vincent's and acid fast organisms were negative. In spite of local therapy, the pain persisted and the ulcer slowly increased in size. A biopsy of the tongue lesion was diagnosed as "granuloma." Following the biopsy the wound remained quite indolent and very painful.

The remainder of her previous medical history was not contributory. She had lived in or about Philadelphia all of her life. There was no history of contact with animals.

Temperature was 98° F., pulse rate 80, respirations 20, blood pressure 130/80, weight 137 pounds. Over the tip of her nose there were a few dilated venules. Her skin color was normal. On the left anterolateral aspect of her tongue there was a rather deep granulating wound, measuring 2 x 1.5 cm., covered by a light gray exudate. There was no significant lymphadenopathy. A moderate general diffuse cystic enlargement of the thyroid was present. Over the skin of the upper chest both anteriorly and posteriorly there were many small papillomas, light chocolate in color. No other areas of pigmentation in the skin or oral mucous mem-

brane could be seen. The remainder of the physical examination revealed no further abnormalities. Urinalysis revealed a normal urine. Hemoglobin was 85%; RBC 4,370,000; WBC 5300 (Diff.: Polymorphonuclears 62%; lymphocytes 37%; eosinophiles 1%). The Kahn test was negative. A Roentgen ray of the chest, and a basal metabolic rate were both normal.

Therapy consisted of a high vitamin diet, and saturated solution of potassium iodide 5 drops 3 times a day. Within a few days she stated that she felt much better and that the pain in her lingual ulcer had almost completely disappeared. As the granulating wound on her tongue was now healing rapidly therapy was discontinued. Two months later, however, a gingival ulcer appeared in the lower incisor area on the buccal aspect. Within a few days this ulcer rapidly increased in size until its diameter was 1.5 cm. The edges were sharp, and the center was deeply excavated exposing about 50% of the cervical portion of the 2 lower central incisor teeth. Potassium iodide was immediately re-ordered —at first 5 drops, then 10 drops 3 times a day. The favorable effect that had been noted with its first administration was not now seen however.

On October 26, 1946 it was noted that her weight was 129 pounds. She had some dyspnea on slight exertion, and it was evident that her condition was becoming worse. There was vague abdominal discomfort. The gingival ulcer was showing no tendency to heal and it was very painful. On January 24, 1947 she was admitted to this hospital because of the onset of fever, and her poor general condition. Weight on admission was 123 pounds. Blood pressure was 120/80. Temperature was 100° F. The liver was now palpable 10 cm. below the right costal margin. It was not tender and the edge was smooth. The remainder of the physical examination revealed no significant change.

Chest Roentgen ray and gastro-intestinal Roentgen ray study were normal. Smears from the gingival ulcer showed some Vincent's organisms but no acid fast organisms were demonstrated. The blood count and sternal marrow smear were normal. The sedimentation rate was 55 mm. per hour. Serum protein was 5.5 gm. %; with 3.3 gm. of albumin and 2.2 gm. of globulin. Urine examinations were consistently negative, and no Bence-Jones protein was found.

On February 12, 1947 her weight was 117 pounds. An irregular fever, varying between 100° and 102° F. was present. Anorexia and weakness were striking. A gingival ulcer which had appeared on the buccal aspect in the region of the 2nd right upper molar and the ulcer in the incisor area remained extremely painful and were uninfluenced by treatment.

During the latter part of February the asthenia increased, and an additional ulcer appeared on the hard palate. It was noted that the blood pressure was falling, now being 90/70. Skin tests to blastomycin, sporotrichin, coccidioidin, and histoplasmin were reported as negative. The patient lost ground very rapidly. Sodium chloride, orally and intravenously, and adrenal cortical extract were ineffective in raising the blood pressure. Death occurred March 2, 1947. It was thought that the symptomatology and clinical course were compatible with the diagnosis of: (1) Histoplasmosis; (2) acute adrenal failure. Culture of the oral lesions (reported several days) gave *Histoplasma capsulatum*.

Autopsy (5 hours after death). The body weighed 48 kg. The principle gross findings were: (1) bilateral enlargement and massive caseation necrosis of the adrenal glands; (2) miliary tubercle-like structures disseminated throughout the lungs, liver, spleen, kidneys, and lymph nodes, and (3) gingival ulcers. Ulcerated lesions were present on the hard palate, and on the gum adjacent to the lower incisor teeth. The tongue appeared normal. There was a diffuse colloid goiter. The *heart* weighed 170 gm. and had the appearance characteristic of brown atrophy. The *lungs* were bulky and emphysematous. The cut surface was diffusely studded with minute translucent, grayish miliary nodules. The *liver* weighed 1430 gm. The cut surface was a homogeneous light tan without distinct lobular markings, and with poorly defined miliary nodules, similar to those in the lung, scattered throughout. The *spleen* weighed 230 gm. Miliary nodules were scattered throughout. The follicles were prominent; the pulp was brick-red. The *adrenals* weighed 60 gm. (left), 65 gm. (right). Both were greatly enlarged and were replaced by firm grayish-white fibrocaseous material with hemorrhagic areas. No tissue suggestive of adrenal parenchyma was noted (Fig. 1). In

FIG. 1.—Gross appearance of an adrenal gland (Case 1). The gland has been sectioned and laid open. Note the caseous material and fibrous tissue which appear to have entirely replaced the adrenal parenchyma.

the *kidneys*, miliary nodules were scattered throughout the cortex, and whitish streaks following the direction of the tubules were present in the medulla. Otherwise their structure appeared normal. Caseous areas were present in the aortic *lymph nodes*. The remaining organs appeared grossly normal.

Microscopic Examination. Adrenals. Very little adrenal tissue was present; most of the tissue was caseous. At the periphery of the caseous tissue there was granulation tissue consisting of proliferating fibroblasts among which round cells and giant cells were scattered. At the junction of the caseous and granulation tissues were large mononuclear cells containing innumerable histoplasma; many of these organisms were acid fast (Fig. 2). *Gingival Ulcer:* The mucosa was absent in places. The papillæ were heavily

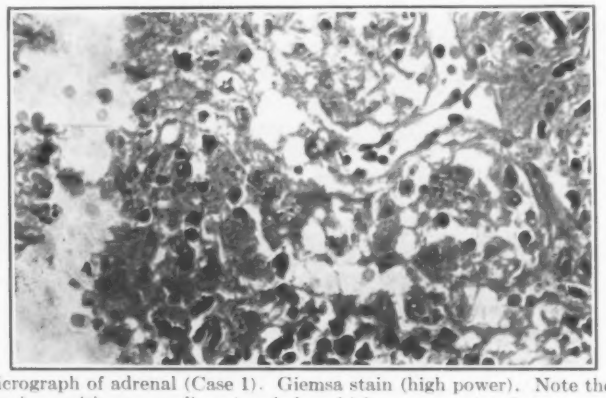

FIG. 2.—Photomicrograph of adrenal (Case 1). Giemsa stain (high power). Note the numerous yeast-like organisms with surrounding clear halo, which are present in large macrophages.

infiltrated with round and plasma cells. In the submucosa there was perivascular round cell infiltration, and numerous organized tubercles containing giant cells of the Langhans type. No organisms of any kind were demonstrated. *Lungs:* Scattered throughout were innumerable round, well-formed nodules consisting of clustered epithelioid cells arranged in no particular pattern. About the periphery of the nodule was a moderate number of lymphocytes; a few polymorphonuclear leukocytes were scattered throughout the lesion. Some nodules contained central giant cells, frequently of the Langhans type. No organisms of any kind were demonstrated in the lesions. *Spleen:* The pulp was pep-

pered with nodules very similar to those described in the lung. Organisms were not seen. *Liver:* There was atrophy of the parenchymal cell cords. Scattered throughout were miliary nodules less well defined than those in the lung. Epithelioid cells were less prominent. The lesions consisted principally of necrotic hepatic cells and polymorphonuclear leukocytes. A few eosinophils were present in the lesions. Giant cells were very rare, and those seen had the appearance of the foreign-body type of cell. Organisms were not seen. *Heart:* A few granulomatous nodules similar to those seen in the lung were scattered throughout the myocardium. *Kidney:* In the cortex, lesions were found similar to those in the lungs, but less well defined. In the pyramids there were large clusters of epithelioid cells and polymorphonuclear leukocytes which tended to follow the direction of the collecting tubules. *Lymph Nodes:* Were virtually replaced by innumerable miliary granulomata similar to those in the lungs. *Final Diagnosis:* Histoplasmosis, producing massive caseous necrosis of both adrenal glands, disseminated granulomata in heart, lungs, liver, spleen, kidneys, lymph nodes, and ulcerating granulomata of oral mucosa.

Case 2. Mrs. M. H., a 41 year old white farmer's wife, gave a history of generalized intermittent headaches for 15 years. On April 21, 1947, she had been struck on the head in the right frontal region by a rake handle; the skin was not broken. Subsequently she was nauseated and vomited in the mornings. Vision became blurred in the left eye, and the headache became worse, radiating over the left side of the head. Because of excessive fatigue and weakness, she was in bed for 5 weeks before being admitted, on June 6, 1947, to the Geisinger Hospital, to which we are indebted for the following information:

On admission, physical examination revealed an obese well-developed white female not appearing ill. Temperature was normal; blood pressure was 135/80 in both arms. Eye examination revealed 20/25 vision in the right eye; vision in the left eye enabled her only to count fingers at 2 feet. There was a ciliary flush in the left eye with débris on the posterior corneal surface and stringy floating vitreous opacities. Enlarged, diseased tonsils were found; the mouth was edentulous. The remainder of the physical examination, including a neurologic examination, revealed no further abnormalities. Lateral skull and mastoid films were normal. Lumbar puncture on June 9 revealed clear, colorless fluid under an initial pressure of 190 mm., that rose to 410 mm. on jugular pressure, followed by prompt fall. The fluid contained 51 cells per c.mm., mostly lymphocytes, with 150 mg. of protein per 100 ml. Blood sugar was 115 mg. per 100 ml. Repeated urinalyses were normal. A diagnosis of bilateral anterior and posterior uveitis and possible brain abscess or tumor was made.

After a course of 40,000 units of penicillin every 3 hours, she was discharged improved. At home her vision grew worse, and by July 10 she was unable to walk due to weakness of the legs. She was irrational, confused, and mentally sluggish. On July 17 she was brought to this hospital.

Systemic review on admission here revealed a history of a chronic cough that had lasted for many years, productive of ½ cup of white sputum daily. The patient had always been overweight. She had suffered with nocturia and mild leukorrhea, and had had chronic backache for many years. She had undergone appendectomy and right oöphorectomy in 1932. Family history was not contributory.

Physical examination revealed an obese, cyanotic white female. Blood pressure was 110/80, pulse 80 and weak, respirations 24, and temperature 98° F. Tonsils were hypertrophied, and the pharnyx was injected. Neurologically, she was incoherent, depressed, torpid and stuporous. The left pupil was dilated and fixed, the right was normal. There was questionable weakness of the right arm. Sensory perception appeared normal. The left corneal reflex was missing, otherwise all reflexes were normal. Tentative diagnosis was brain abscess or subdural hematoma.

Ophthalmologic consultation described the left eye as showing marked ciliary flush, slight haziness of the cornea, normal finger tension, many pigmented keratitic precipitates and massive vitreous exudation through which no fundus details could be seen except for a large white choroidal lesion in the upper temporal midperiphery. This was similar in appearance to the lesions seen in tuberculous uveitis.

Laboratory findings: hemoglobin 70%; leukocyte count, 14,000 per c.mm.; blood

urea nitrogen, 49 mg. per 100 cc.; fasting blood sugar 62 mg. per 100 cc. Urinalysis: specific gravity 1.008, acid, no albumin or sugar, 2 to 3 RBC and 10 to 15 WBC per high power field, no casts, occasional epithelial cells. Urine culture showed an intermediate strain of E. coli. Kolmer and Kline tests negative.

Course in hospital: Patient remained in much the same condition during her first hospital day. Suddenly and without warning, 21 hours after admission, she expired.

Autopsy (2 hours after death). The body was that of an obese white female weighing 81 kg., and measuring 160 cm. There was marked generalized cyanosis. *Heart:* weighed 270 gm. and appeared normal except for mild coronary sclerosis. *Lungs:* Right weighed 280 gm., left 230 gm. While these appeared grossly normal, microscopically they showed moderate atelectasis, with areas of mild compensatory emphysema. No organisms were seen. *Liver:* Weighed 1450 gm. and appeared normal both grossly and microscopically. *Spleen:* Weighed 280 gm. It was a little larger and softer than usual, with purplish-gray surface. On cut section the pulp was brick-red and the trabeculæ and follicles distinct. Microscopically, it appeared normal. *Pancreas:* Appeared normal grossly and microscopically. *Adrenals:* The right weighed 22 gm., the left 30 gm. Both were increased in consistency. On cut section there was an escape of thick whitish purulent liquid, which was odorless. The normal adrenal architecture was absent, cortex and medulla of both glands apparently being entirely replaced by the soft white material, surrounded by an ill defined firmer capsule (Fig. 3). Microscopically, the entire gland was seen to be replaced by eosinophilic, necrotic tissue containing many round, clear

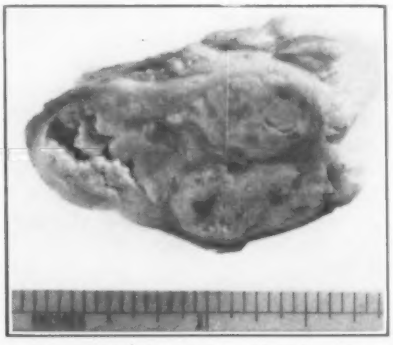

Fig. 3.—Gross appearance of an adrenal gland (Case 2). The gland has been sectioned. Note the large areas of caseous material separated by fibrous bands.

spaces, varying in diameter up to 30 micra; in most of these there were round refractile bodies with evidence of internal structure. A few of these took the hematoxylin stain, but most were colorless (Fig. 4). There was much variation both in their size and refractility. In addition to the caseation necrosis there was a fibrous reaction in which actively proliferating fibroblasts appeared to be walling off the caseous tissue. In the fibrous zone there were collections of lymphocytes and giant cells of the foreign-body type (Fig. 5). No recognizable adrenal tissue was found. Ziehl-Nielsen stains of the sections revealed no acid-fast bacilli. The refractile bodies did not take this stain. Gram stains tinted some of the organisms a faint blue. India Ink preparations made from scrapings of the cut surface showed doubly refractile, round bodies, varying in diameter from 5 to 30 micra, surrounded by a thick clear capsule. Many of the organisms showed budding, with dumb-bell and figure-eight forms. Some contained refractile bodies 3 to 5 micra in diameter, often arranged in clusters placed eccentrically in the cell. These organisms satisfied the morphologic description of *Cryptococcus neoformans* (*Torula histolytica*); their identity was confirmed by Dr. Fred Weidman. *Kidneys:* The right weighed 120 gm., the left 130 gm. They appeared grossly normal. Microscopically, the capsule of the right kidney was somewhat thickened, with small collections of polymorphonuclear leukocytes scattered through the cortex. Adjacent to one such

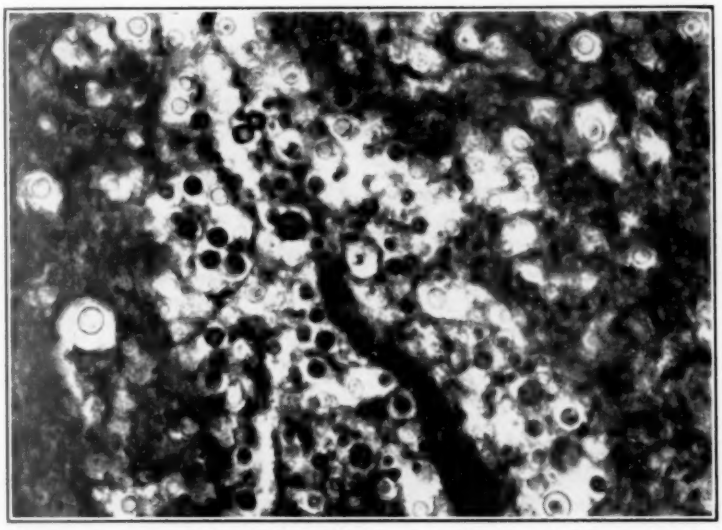

FIG. 4.—Photomicrograph of adrenal (Case 2). Hematoxylin-eosin (high power). Note the round refractile organisms with clear enveloping halo. Some organisms have taken the hematoxylin stain; others have not. The organisms lie free in the tissue.

collection, embedded in the necrotic wall of a tubule, was a cluster of *cryptococci*. These were the only organisms found in the kidneys. The left kidney showed less capsular thickening, but similar cell collections. Both kidneys showed numerous collections of granulocytes lying in and around the collecting tubules. The glomeruli were essentially unchanged. There was an occasional pigment cast. Acid fast stains of the sections revealed no acid fast bacilli. *Brain:* The brain weighed 1250 gm.; the meninges and

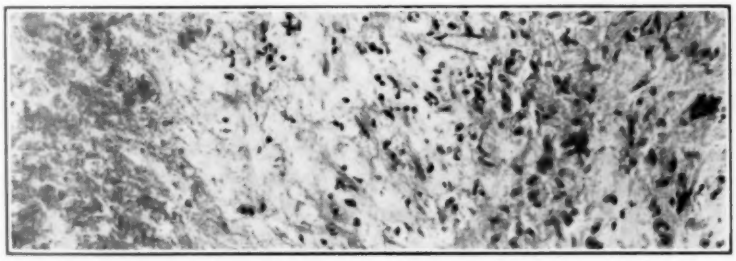

FIG. 5.—Photomicrograph of adrenal (Case 2). Hematoxylin-eosin (high power). Note the fibrous tissue reaction, the giant cells, and the necrotic area.

brain substance appeared grossly normal. Microscopically, some of the sections showed a chronic meningitis consisting of round cell infiltration, rare giant cells, and proliferation of fibroblasts. In the adjacent cortex, were round bodies about the size of torula which took the hematoxylin stain. No capsules or refractile forms could be demonstrated. All other organs appeared grossly and microscopically normal. Permission for the removal of the eyes was not obtained. The final diagnosis was torulosis, causing massive necrosis of both adrenals, and focal lesions in the kidneys. It is probable that the eye and meningeal lesions were also manifestations of torulosis.

Comment. Among the multiplicity of symptoms caused by a disseminated fungus disease, the diagnostician is apt to overlook possible indications of failure of the adrenal glands. Such symptoms as weakness, anorexia, weight loss and dehydration are not diagnostic in themselves,

and indeed may be merely results of a febrile state. Except in the terminal stages, however, both histoplasmosis and torulosis are characterized by a low-grade fever; the marked weakness and enormous weight loss in those cases that show massive adrenal destruction at autopsy are out of all proportion to the febrile response. While terminal fall in blood pressure is frequent in the cases of adrenal destruction caused by these diseases, the sign appears too late as a rule to be clinically helpful. Bronzing of the skin was noted in but 1 case (Case 5, Table 2).

The 2 cases presented in the present communication both showed definite symptoms of adrenal insufficiency. These were recognized during life in the first case, but not in the second. In Case 1 the disease appeared to start as a localized tongue lesion, and it was not until some time later that dissemination was evident. At this time marked weakness, anorexia, and weight loss were noted despite a fever of but 100° F. It was not until 2 weeks before death that the blood pressure fell to 90/70. Therapy with adrenal cortical extract, and sodium chloride instituted at that time was ineffective.

The only symptoms presented by Case 2 which might have placed the adrenals under suspicion from the start were excessive weakness and fatigue which caused the patient to remain in bed for the 5 weeks prior to her admission to the Geisinger Hospital. Indeed her weakness was so severe that she was unable to stand long enough for the performance of the Romberg test. The peculiar cyanotic color of the skin may possibly also be attributable to the adrenal failure. Despite the complete adrenal destruction, however, a fall in blood pressure was not noted.

Of interest is the fact that in the cases of adrenal failure due to histoplasmosis (Table 2) a ratio of 2 males to 1 female is found. This is the same ratio noted in Addison's disease from all causes.[5] The age group (39 to 63) is somewhat older than that given for Addison's disease (30 to 50).[5] All cases in the series belonged to the white race.

Although 76% of the cases of adrenal histoplasmosis showed caseation, only 28% of those of adrenal torulosis did. Although this series is too small to draw conclusions as to pathogenesis, it is interesting to note that the caseous reaction may be an allergic one,[19] and that histoplasma capsulatum is capable of producing sensitization,[8] while cryptococcus neoformans frequently is neither antigenic, nor allergenic.[11]

Tuberculosis and other granulomatous processes such as Hodgkin's disease have been observed to accompany both histoplasmosis and torulosis (Cases 1 and 6, Table 2). It is well known that the demonstration of tubercle bacilli in sections is often very difficult. For these reasons it has been suggested that many cases of both histoplasmosis and torulosis may be but the secondary invasion of yeasts in pre-existing tuberculous lesions—a concept which would explain the close similarity of the lesions found in the 3 diseases.

Summary. 1. Case reports available to us of adrenal involvement by *Histoplasma capsulatum* and by *Cryptococcus neoformans* (*Torula histolytica*) are reviewed.

2. Adrenal insufficiency due to massive destruction of the glands is a complication of both histoplasmosis and torulosis, being more common in the former.

3. To our knowledge, the first case of adrenal insufficiency due to torulosis and the ninth case due to histoplasmosis are herewith presented.

4. Excessive weakness appears to be the earliest symptom of adrenal destruction caused by these two diseases.

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ROENTGEN THERAPY IN TRAUMATIC MYOSITIS OSSIFICANS

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The present study was undertaken in order to determine the efficacy of roentgen therapy in traumatic myositis ossificans. In the recent literature there are few reports of its use in this condition. Because of the excellent results obtained in the treatment of bursitis we were induced to try it in a series of patients with traumatic myositis ossificans. The rationale of employing this method in the treatment of myositis ossificans traumatica is believed to be on a sound basis, since the condition begins as an inflammatory reaction in response to hemorrhage produced by trauma.

Etiology. The terms myositis ossificans traumatica, ossifying hematoma and calcifying hematoma have been used interchangeably to describe the process of calcification and ossification occurring within muscle tissue in response to trauma. Although the condition tends to become asymptomatic and to regress, it may be accompanied by disability and discomfort for varying periods of time and may even be progressive. It occurs most commonly in young men. The initiating factor which is most frequently described in the recent literature is acute trauma. Particularly common sites of involvement are the muscles of the anterior aspect of the thigh following a blow, and the elbow region following dislocation. Less frequently the trauma is of chronic nature. Billroth (quoted by Geschickter[7]) in 1885 described myositis ossificans traumatica under the term "rider's bone," since it occurred in the adductor muscles of the thighs of cavalrymen. Later a similar condition was described in the deltoid muscles of infantrymen. In our series chronic irritation played a rôle in 1 case. However, the majority were in young men of college age who suffered injury while playing football, basketball, or participating in other sports. In 1 case myositis ossificans developed about the elbow joint following dislocation.

Pathology and Pathogenesis. A number of theories have been offered to explain the pathogenesis of myositis ossificans traumatica. Carey[5] has summarized most of these theories as follows: (1) hemic, which maintains that hemorrhagic blood becomes organized and is transformed into cartilage and finally into bone; (2) sesamoid bone, according to which, trauma stimulates the development of sesamoid bones; (3) bone formation within muscle as a result of detached periosteal flaps; (4) subperiosteal dissemination, which holds that when periosteum ruptures it allows subperiosteal osteogenetic cells to proliferate and invade the musculature; (5) hematogenous infection; (6) synovial escape, which gives consideration to the possibility of synovia escaping into soft parts; (7) metaplasia of intramuscular connective tissue into bone; (8) combined metaplastic and periosteal theory; (9) underlying diathesis or dyscrasia. Another theory was added by Hirsch and Morgan,[9] who believe that endochondral bone formation can take place as a result of stimulation of fibrocartilage by trauma. They find fibrocartilage to be a normal tissue constituent in areas where traumatic myositis ossificans occurs.

It is rather generally accepted that myositis ossificans begins as an inflam-

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matory process in response to hemorrhage due to tears and contusions of muscles, muscle insertions, periosteum and blood vessels. Thorndike[18] logically outlined the pathogenesis as follows: (1) a severe deep muscle contusion accompanied by the tearing of muscle fibers and capillaries and loosening of periosteal cells, (2) hemorrhage with accompanying inflammatory reaction that one would expect in hematoma formation, and (3) hematoma absorption in which ossification takes place.

Histologically myositis ossificans has been studied in various stages and by various workers. Geschickter and Maseritz[8] in analyzing 25 cases found the presence of hemorrhage, the organization of hemorrhage, myxomatous tissue, angiomatous tissue, calcification en masse, hyalinization of capillaries and degeneration of muscle; any combination of these findings were seen accompanying bone formation in a section or group of sections. Degeneration of muscle, hyperplasia of connective tissue and organization of hemorrhage were the earliest histological manifestations which they observed. They noticed a tendency to capsule formation which was simultaneous with calcification en masse in the inner portion of the young connective tissue. Islands of osteoid tissue which became invaded and surrounded by osteoblasts and marrow spaces were found later. With advancing bone formation they observed partially formed osteoid spicules and more completely formed spicules typical of those seen in the process of cancellous bone formation. Cartilage was present in about one-fourth of the instances. Geschickter and Maseritz[8] felt that osteoblastic formation and calcification were the probable changes which preceded bone formation. Hirsch and Morgan[9] saw acute exudative inflammation of the tissues and edema and hemorrhage in the early stages as a sequela of the trauma; in later stages they found scar-like connective tissue or granulation tissue with masses of bone and cartilage in varying amounts. Shipley,[17] Pack and Braund,[15] Butler and Woolley,[4] and others have reported the development of malignant neoplasm in myositis ossificans.

In one instance in this series surgical removal of a 3 by $2\frac{1}{2}$ inch calcified hematoma from the substance of the right vastus intermedius was done with subsequent recurrence. Histologically the removed mass showed areas of degenerating muscle surrounding an area of laminated bone and well formed bone spicules with marrow spaces composed of loose fibrous tissue infiltrated by lymphocytes and phagocytes filled with some blood pigment (Fig. 3).

Clinical Findings. The most constant symptom is pain which may be of short duration or persistent or progressive for varying periods of time. On the other hand pain does not necessarily accompany the appearance of myositis ossificans traumatica. Limitation of motion may result particularly when the site of involvement is near a joint or a muscle insertion. The earliest physical finding consists of a doughy swelling which increases in size and becomes more firm.

Roentgenographically, calcification may appear from 1 to 4 weeks after injury. Lewis[12] claims that bone formation reaches its maximum and ends within 6 weeks and then either regresses or remains stationary. Geschickter and Maseritz[8] state that maximum bone formation occurs in 10 weeks to 20 months. Thorndike[18] followed a series of 25 cases for a period of years to determine the final outcome of the ossification. Nine cases (36%) were found to have absorbed spontaneously. Some of these regressed as early as 2 months after their discovery, while another case showed only partial resorption in 5 years. Thorndike concluded that the criteria for absorption seem to be mainly size and location as well as individual diathesis. The smaller areas of calcification and those in the upper extremities, with the exception of those about the elbow, seem to have a greater tendency to disappear. Those in the belly of a muscle tend to

become dormant and painless even in severe cases when regression is incomplete. Those near muscle insertions may become dormant but tend to interfere with function. Hobart[10] believes that continued irritation as by movement will tend to make the process progressive.

In our series of cases pain was present in all and usually it was the chief symptom which led the patient to seek medical advice. Limitation of motion was the chief complaint in a few and was associated with pain to some extent in all. The duration of symptoms varied from 2 weeks to 1 year. Soft tissue swelling and roentgenographic findings were present in all patients.

Treatment. The prophylactic measures most widely advocated are the avoidance of massage, the application of cold and the use of a compression bandage immediately after an injury, thus attempting to reduce hemorrhage. Böhler[3] goes so far as to say that he believes myositis ossificans traumatica occurs as the result of massage following an injury rather than of the injury itself. Thorndike[18] states that evacuation of a hematoma in its early stages is contraindicated.

Treatment of myositis ossificans traumatica after calcification has occurred has consisted of physical therapy and surgical removal. Early surgical removal has been condemned because of the tendency of the lesion to recur. Thorndike[18] recommends operative removal only in those cases where ossification occurs near a joint or in the origin or the insertion of a muscle, or where function is permanently impaired, and then only from 12 to 24 months after injury.

The use of Roentgen rays for the treatment of myositis ossificans has been described by Jüngling[11] and others.[1,2,13,14,16] Chevrier and Bomriot[6] have treated dislocation of the elbow prophylactically with Roentgen rays on the theoretical basis that inflammatory processes would be influenced and the myositis ossificans therefore prevented. The beneficial action of prophylactic Roentgen therapy is difficult to prove for the obvious reason that many unirradiated sites of injury will not become involved with myositis ossificans. Jüngling[11] treated with Roentgen rays early cases in which the inflammatory process was likely to be still present. He believed that results could not be expected in a permanent inactive process which causes only limitation of mobility of a joint but that Roentgen therapy might still be used during the first 3 months for the reason that during this time there are still inflammatory changes present.

The technique employed in the use of Roentgen rays in treating the patients of our series consisted of doses of 150 r to 200 r (in air) delivered to 1 or 2 fields daily or every other day for 3 or 4 treatments. When indicated, a second series was given in 4 to 6 weeks and a third in 2 to 4 months after the first course. In 5 cases, only 1 course was necessary. In the other 5 cases 2 or 3 courses were given. Technical factors were 175 or 400 kv., 50 cm. FSD and half value layers of 1.05 mm. Cu. and 2.4 mm. Cu. respectively. The field size was large enough to include a wide zone about the area of calcification.

Results. The accompanying Table 1 outlines the significant clinical and roentgenographic findings and the results of Roentgen therapy in each of the 10 cases. Complete relief of pain occurred in all cases following treatment to the area involved by traumatic myositis ossificans. Relief of pain was noted within 4 to 6 weeks following Roentgen therapy. Often the improvement was dramatic and began as soon as 2 or 3 days after treatment. The following case illustrates this.

Case Reports. Case 1. W. W., a police officer, age 34, was first seen on Nov. 16, 1944, at which time he complained of an exquisitely painful lump "as sore as a boil" on the posterior aspect of his left thigh. The pain had begun 6 months previously and had become progressively more severe. He had no history of acute injury. However, his duties included riding in a squad car a good portion of the day. Considerable aggravation of the pain resulted when he shifted

TABLE 1.—CLINICAL DATA IN 10 CASES OF TRAUMATIC MYOSITIS OSSIFICANS

Name	Age	Site	Etiology	Symptoms	Duration	Roentgenologic findings	Therapy	Symptomatic results	Roentgenologic results
D. F.	20	Lt. elbow	Dislocation	Severe pain and marked limitation of motion	3 mo.	Calcification, ossification in periarticular soft tissue lateral to elbow joint and lower end of humerus	3 courses 3 x 200 r lat. elbow	Complete pain relief and improved motion within 4 wks. but persistent flexion deformity	60 % decrease in size after first course, slight further decrease following subsequent courses.
K. P.	22	Ant. rt. thigh	Injury	Pain and limitation of motion	3 mo.	Calcified mass in ant. aspect of rt. thigh	3 x 150 r ant. rt. thigh	Complete pain relief and increased motion within 4 weeks	No decrease in size but increased density.
K. D.	22	Antero-lat. rt. thigh	Recurrence after surgical removal	Marked limitation of motion and pain	2 wks.	Calcification in soft tissue anterior to shaft of rt. femur	2 courses 3 x 150 r 4 x 200 r	Complete pain relief and considerable increase in motion within 6 weeks	Slight decrease in size of calcification which became denser.
J. Z.	18	Lt. thigh	Basketball injury	Pain and limited motion	4 wks.	Laminated calcification in soft tissues along the lateral side of the mid shaft 8 cm. long	3 x 150 r.	Complete pain relief and return of motion to normal within 4 weeks	Complete absorption of calcium within 4 wks. after treatment.
T. T.	19	Lt. shoulder	Surfboard injury	Persistent, progressive pain	1 yr.	Semilunar shaped calcification below and ant. to glenoid fossa	2 courses 3 x 150 r A/p lt. shoulder	Complete relief of pain within 6 weeks	Slight absorption of calcium.
R. M.	16	Quadriceps lt. thigh	Injury	Severe pain	3 mo.	Calcified mass in soft tissues in ant. rt. thigh 17 by 7 cm.	4 x 150 r ant. thigh	Complete pain relief within 4 weeks	Decrease in size and more bony appearance of calcification.
R. F.	16	Quadriceps rt. thigh	Toboggan injury	Pain	3 wks.	Calcification in soft tissues ant. to shaft of femur 2.5 cm. long	2 courses 3 x 200 r ant. thigh	Complete relief of pain within 4 weeks	Complete absorption of calcium within 6 months.
J. L.	20	Ant. lt. thigh	Football injury	Pain	4 wks.	Calcification in soft tissues anterolat. to mid shaft of femur 3 by 6 cm.	3 x 150 r	Complete relief of pain within 6 weeks	Moderate decrease in size of calcification.
W. W.	34	Post. lt. thigh	Chronic irritation associated with occupation	Very severe pain and tenderness	6 mo.	Calcification posterior to shaft of lt. thigh 2.5 cm. in diameter	3 courses 3 x 150 r	Complete relief of pain within 4 weeks	Decrease in size of calcification.
D. R.	18	Ant. rt. thigh	Basketball injury	Pain	2 mo.	Laminated calcification soft tissues in anterolat. rt. thigh 5 by 15 cm.	2 courses 3 x 150 r	Complete relief of pain within 6 weeks	Reduction in size of calcified mass by one-third.

gears in his car. On examination a hard tender mass was found on the posterior aspect of the left thigh. Roentgenograms showed a rounded irregular calcific density, measuring approximately 5 cm. in length, in the soft tissues of the posterior aspect of the left thigh at the junction of the middle and upper third of the femur and having the appearance of myositis ossificans (Fig. 1, *A*). On 3 consecutive days he received 150 r (in air) to the affected region. Technical factors were 400 kv., 5 ma., 50 cm. FSD, HVL= 2.4 mm. Cu. Improvement began

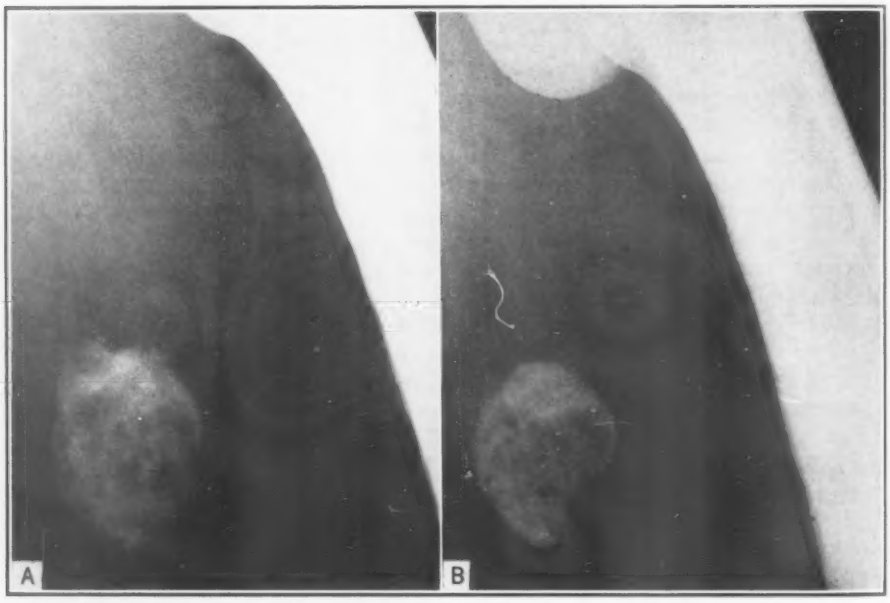

FIG. 1.—*A*, myositis ossificans traumatica before beginning Roentgen therapy; *B*, approximately 3 months after treatment with Roentgen rays. (Case 1.)

2 or 3 days following treatment. At the end of 4 weeks all pain had disappeared and on roentgenographic examination the calcified mass was found to be reduced to about two-thirds its original size. A second and third series were given at a 4 and an 8 week interval. Roentgenographic evidence of further reduction in the size was observed about 3 months after the first examination (Fig. 1, *B*). Symptoms have not recurred.

Limitation of motion was associated with pain to a lesser or greater extent in all cases. When pain was relieved, function usually returned promptly to normal. However, in 4 cases a limitation of motion was apparently due to mechanical interference resulting from the abnormal calcification and ossification within the muscle tissue. In these cases improvement of function usually lagged behind pain relief and as a rule a second or even a third course of therapy was given. In all but one, in whom a flexion deformity persisted, considerable or complete improvement of motion followed one or more courses of Roentgen therapy. The following case is of interest from several points of view, but particularly because of the improvement of marked limitation of motion.

CASE 2. K. D., a 22 year old white male, fell on Dec. 23, 1938, and struck the anterolateral aspect of the lower portion of his right thigh against an iron bar. Swelling and pain followed and persisted. His family physician prescribed hot and cold applications and elastic bandage, and 3 weeks later he aspirated hemorrhagic fluid from the site of injury. On Feb. 4, 1939, the patient was first seen in the Orthopedic Department of The State of Wisconsin General Hospital. He complained of pain in the right thigh and

limitation of motion in the right knee joint On examination a hard, fixed, tender mass measuring 5 inches in length was found along the anterolateral aspect of the lower third of the right thigh. Flexion of the right knee was limited to 30° both actively and passively, neither could he completely extend his leg. Roentgenographic examination showed a considerable amount of calcification in the soft tissues anterior to the junction of the middle and lower thirds of the shaft of the right femur and having the appearance of myositis ossificans (Fig. 2, *A*).

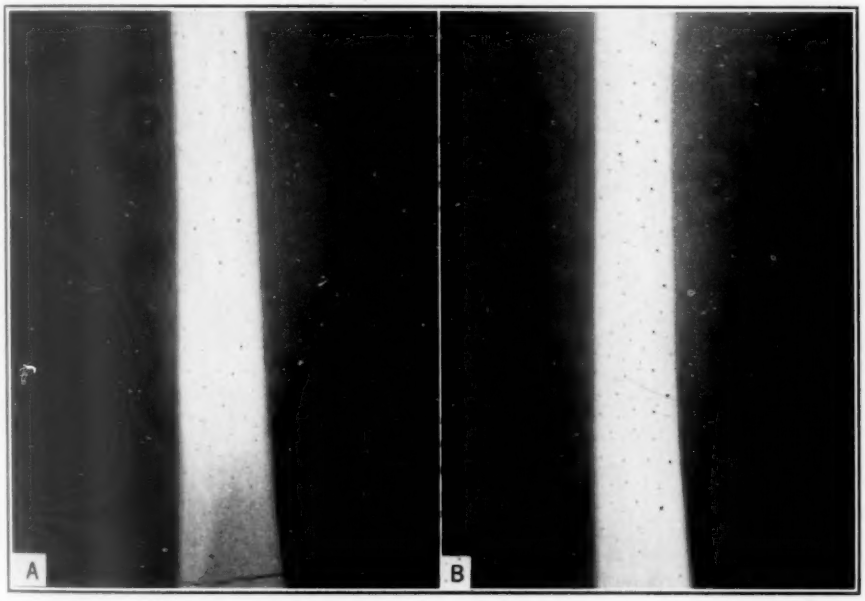

FIG. 2.—*A*, myositis ossificans traumatica before treatment; *B*, after surgical removal. (Case 2.)

The patient was referred to us on Feb. 9, 1939, for Roentgen therapy. After the second treatment, however, the surgeons decided to remove the calcified mass and consequently the course of Roentgen therapy was not completed. The microscopic study of the removed tissue showed degenerating muscle surrounded by an area of laminated bone. The bony spicules were well formed and the marrow spaces were composed of loose fibrous tissue infiltrated by lymphocytes and phagocytes filled with blood pigment. The histological diagnosis was myositis ossificans (Fig. 3). Under anesthesia before surgical removal flexion was limited to 40°; after removal it was increased to 120°. On Feb. 12, 1939, a roentgenogram showed that the calcified mass had been removed completely (Fig. 2, *B*).

On March 1, 1939, the patient returned again with flexion at the knee joint limited to 40° and inability to completely extend the leg. Pain was slight to moderate. A roentgenogram showed recurrence of the myositis ossificans (Fig. 4, *A*). Between March 1 and March 4, he received a course of Roentgen therapy consisting of 3 times 150 r (in air) to the involved area. Technical factors were 175 kv., 50 cm. FSD and HVL of 1.05 mm. Cu. Five weeks later on April 20, his ability to flex the right knee had increased from 40° to 120°. Pain was present only when pressure was applied over the area. Roentgenograms showed a slight decrease in the size of the calcification. A second series of 4 times 200 r, using the same technical factors, was given. Further symptomatic improvement occurred and there has been no recurrence of symptoms to our knowledge. Roentgenograms on June 6, 1939, showed a smoothing of the area of calcification and a general increase in density but no resorption of calcification or extension of the process (Fig. 4, *B*).

Comment. Follow-up roentgenograms were obtained in all cases. In 2 cases the calcifications were completely absorbed. In one instance the absorption took place within 4 weeks after Roentgen therapy and within 2 months after the injury, and in another instance absorption took place within 6 months after treatment and within 7 months after the injury. It is noted that in these 2 cases treatment was given within 4 weeks after the trauma. With the exception of one case, at least a slight decrease in the size of the calcified area was observed. An increased density and a sharper and smoother outline was consistently noted in roentgenograms taken after therapy had been administered. However, since it is well known that spontaneous absorption and decrease in size of myositis ossificans does occur, the described roentgenographic findings cannot necessarily be attributed to irradiation. Symptomatic improvement could not definitely be associated with the amount of decrease in size of the mass.

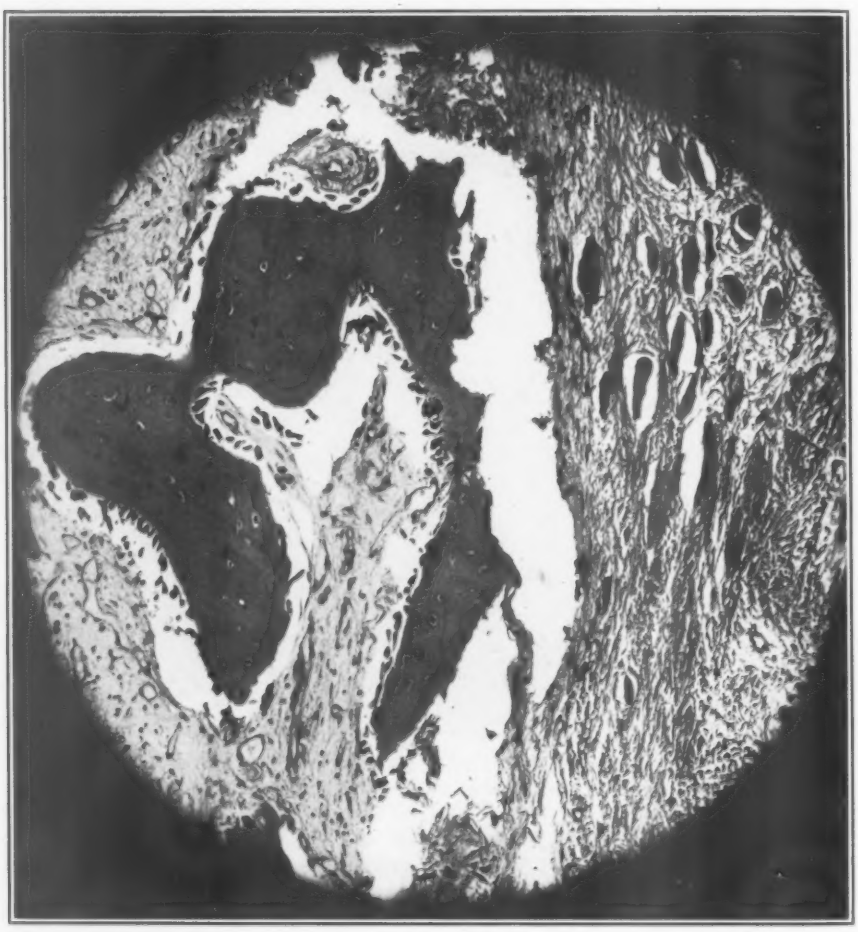

Fig. 3.—Photomicrogram of the surgically removed tissue. (Case 2.)

Although the results of treatment are difficult to evaluate, particularly in a small group of cases, because of the tendency of myositis ossificans to regress and become inactive, beneficial results in this series of

cases appeared to be definitely related to treatment with Roentgen rays. Since half of the patients had symptoms which were persistent or progressive for at least 3 months, it is unlikely that the prompt symptomatic relief which occurred following Roentgen therapy happened to coincide with what might have been spontaneous regression. Most convincing in this respect is Case 2, in which the signs and symptoms of myositis ossificans recurred following surgical removal, yet after treatment with Roentgen rays complete relief of pain and considerable increase of motion resulted. The action of Roentgen rays in myositis ossificans traumatica is believed to be similar to that in chronic bursitis and other inflammations. As in bursitis, it is likely that the earlier in the course of the disease treatment is given the better the results will tend to be. When symptoms of pain and limitation of motion persist or are progressive, it undoubtedly indicates that inflammatory changes are still present and consequently, improvement may be expected even where symptoms are of long duration. Since traumatic myositis ossificans can be very disabling to otherwise healthy young men and since the only other adequate method of treatment is surgical and is often followed by recurrence, particularly if done in less than a year following the onset, we believe that the beneficial results obtained in this group of cases justify further trial of Roentgen therapy in myositis ossificans traumatica.

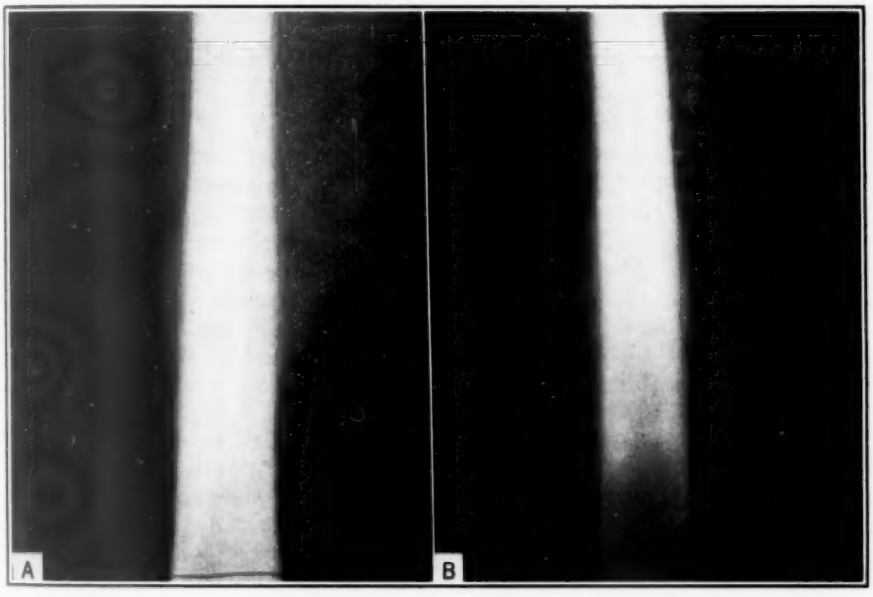

FIG. 4.—*A*, recurrence 2 months following operation; *B*, approximately 3 months following Roentgen therapy. (Case 2.)

Summary. 1. A brief review of the literature concerning the etiology, pathology and pathogenesis of myositis ossificans traumatica is given.

2. Ten cases of symptomatic myositis ossificans traumatica treated with Roentgen rays are presented.

3. Following Roentgen therapy complete relief of pain resulted in all cases. Limitation of motion was markedly improved or restored to normal in all but one in which only slight to moderate improvement of function was obtained.

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THE PARATHYROID: A STUDY BASED, IN PART, ON SIXTY POST-MORTEM EXAMINATIONS WITH PRESENTATION OF A CASE OF HYPERFUNCTIONING ADENOMA*

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The history of the part played by the parathyroid in disease does not go far. In 1864 Engel described a case of unusual bone disease which von Recklinghausen[41] in 1891 classified with certain of his cases as generalized fibrocystic osteitis and distinguished them from osteomalacia.

As far as one can be certain, the parathyroid was not recognized as an independent anatomic structure until 1880 when the Swedish anatomist, Sandstrom, described the gland and gave it its name. So far as its function is concerned, nothing definite was known until 1891 when the French physiologist, Gley[28] showed that in dogs extirpation of the parathyroid gland led to characteristic manifestations of tetany.

In 1902 Benjamins[14] reported the first case of parathyroid tumor, probably an adenoma. In 1903 Erdheim[25] reported a case which has been recorded in the literature as being the first. However, he refers to the case of Benjamins. Askanazy[11] in 1902–04 published the results of an autopsy of a patient who had suffered from generalized decalcification and found a parathyroid tumor. Later Erdheim drew attention to the relation between the parathyroid and the skeleton. He noted the association between bone disease and enlargement of the parathyroid gland and concluded that this enlargement might be encountered as a consequence. His failure to recognize the etiologic significance of a parathyroid tumor in generalized osteitis fibrosa cystica no doubt retarded progress in the field. In 1925 Mandl,[35] through courage, for the first time removed a parathyroid tumor in a case of bone disease and led the way for other surgeons.

Since 1930 better understanding of hyperparathyroidism and its clinical manifestations has been due largely to the works of Albright and his associates.[1,2,3,4,5,6,7,8] They showed that renal disease was a more common manifestation and that hyperparathyroidism could occur and be recognized in cases in which there was no evident bone disease.

The insidious manner in which a hyperfunctioning parathyroid adenoma exacts its toll over a period of years is well shown in reports from the literature. Only among those clinicians who are alert to its manifold manifestations along the way will early diagnosis be made. The removal of the tumor will cure the disease but the effects of irreparable kidney and bone damage which come about in the late stages may leave little room for rejoicing to either the surgeon or the patient as to the results.

In approaching the subject for this study, the parathyroid gland was studied from various aspects with the plan in mind to portray as clearly as possible certain facts which might be of help to the surgeon. Microsections, made from each of the 60 postmortem dissections, were

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studied with respect to the age of the patient and the anatomical diagnosis.

EMBRYOLOGY.[10,12,21] The primitive pharynx is the source of numerous organs. Most of the developmental complexities occur during the transitional period when the embryo passes from a stage in which the pharynx is arranged for branchial respiration to the stage in which breathing is anticipated. The branchial arches are bar-like ridges separated by grooves which appear on the lateral surfaces of the embryonic head. In the human there are 5 arches separated by 4 external ectodermal grooves. Subjacent to these grooves, the entoderm of the pharynx bulges outward to constitute complimentary pharyngeal pouches. There are 5 sets of pouches, the last being rudimentary and attached to the fourth. The pharynx becomes flattened dorsoventrally and broadened at its cranial end, as a result of which it is triangular in outline. Each typical pouch develops a dorsal and ventral wing.

The inferior parathyroid glands develop from the dorsal wings of the third pharyngeal pouches. They are set free from the pharynx and drawn down by the migrating thymic primordia which develop from the ventral sacculations of the third pharyngeal pouches.

The superior parathyroid glands develop from the dorsal wings of the fourth pharyngeal pouches. Presumably the lateral thyroid primordia develop from the ventral wings of the fourth pouches. However, the main mass of the thyroid develops from the ventral floor of the pharynx from an entodermal pocket forming in the midplane at the level of the first pharyngeal pouches.

As schematically shown in Figure 1, the extent of migration of the superior and inferior parathyroid glands and any relation they may bear to the thyroid and thymus glands may be realized. Parathyroids IV (superior) descend a relatively shorter distance and are usually in close relation to the thyroid gland. Parathyroids III (inferior) descend a relatively greater distance and may be in relation to the thymus. They usually come to rest opposite the lower pole of the thyroid but may extend into the mediastinum or be invested within the capsule of the thymus.

ANATOMY. In these dissections the superior pair were more often found closely applied near the lateral margin posteriorly just above the middle of the body of the thyroid gland. The inferior pair were more often located just below and lateral to the lower pole of the thyroid embedded in loose areolar tissue. (Fig. 2.) On finding one gland, its mate was found ordinarily in a corresponding position.

The weight for each has been given as 0.035 gm., average. Because of their extreme softness, the shape and apparent size varies. Each measures 6 to 7 mm. x 3 to 4 mm. x 1.5 to 2 mm.[36] Most commonly they are flattened, ovo-elliptical structures. In this study the superior gland was usually found to be smaller, flattened, and irregular due to pressure of contiguous structures. Each was contained in a thin filmy capsule. It was not possible always to identify the gland by its color. Usually it was of a putty tan shade. Some had a pink cast like thyroid tissue, and others were grayish-yellow. Occasionally a distinctly brown shade existed. A small blood vessel was seen to branch over the surface of the gland in about 10% of the cases. At times the only means of identifying the gland grossly was by teasing the surface with a needle which brought out its filmy encapsulated form and its soft consistency.

Experience with dissection of the neck has shown that one can identify grossly the parathyroids. However, because of their variation in position they are not always easy to find. They have to be distinguished from: (1) a loosely attached peripheral bud of thyroid tissue (deeper reddish cast identical to that of adjacent thyroid with a firmer consistency); (2) lymph node (usually round, darker in color, and of brittle hardness); (3) encapsulated fatty tissue (soft but of a very pale yellow color); and (4) aberrant thymic tissue which is enveloped by membranous

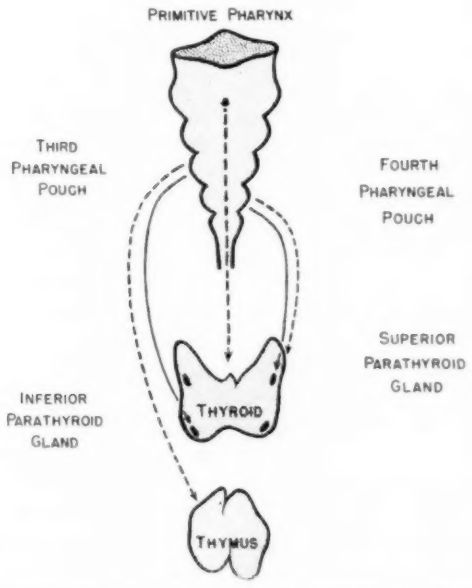


FIG. 1.—Embryology. Descent of the parathyroid glands showing relation to the thyroid and thymus. The inferior parathyroids and thymus take origin from the third pharyngeal pouches, as shown on the left side of the diagram. The superior parathyroids and lateral thyroid bodies take origin from the fourth pharyngeal pouches, as shown on the right side. The main mass of the thyroid develops from the ventral floor of the pharynx about the level of the first pharyngeal pouches. The wider range for the location of the inferior glands along with their possible relation to thymus is appreciated.

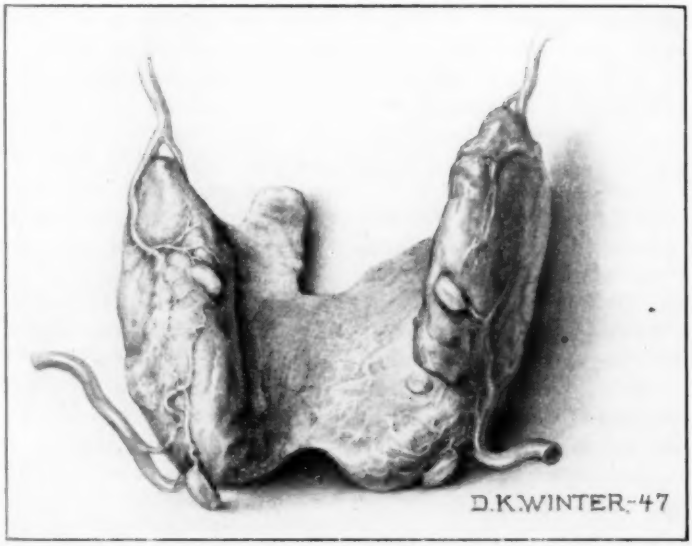


FIG. 2.—Anatomy. Tracheal surface of the thyroid gland to show the 2 pairs of parathyroids as they are often found at necropsy. The blood supply usually is derived from the inferior thyroid arteries.

septa of connective tissue (soft with a pale, dirty grayish-yellow appearance).

HISTOLOGY.[13,17,18,36] The study of the histology of the parathyroid gland in these cases was made on patients whose ages at time of death ranged between 21 and 82 years.

The gland is supported by a thin capsule. Connective tissue strands pass into its substance forming delicate septa. The blood supply, which is rich, most often comes from the inferior thyroid vessels. A vascular twig enters at one point, divides under the capsule, and spreads out along the septa. The nerve supply is scanty and the fibers are thought to be entirely vasomotor.

The parenchyma is composed of anastomosing cords of cells between which the capillaries are located. Often the cells are disposed as continuous masses. Less commonly they form acini of various sizes which may contain colloid-like material. Varying numbers of fat cells are usually scattered among the epithelial cells.

The chief or principal cell makes up the bulk of the gland. It is polyhedral in shape and poorly outlined. The cytoplasm is usually scant and faintly acidophilic. Unstained areas, especially about the nucleus, sometimes give the appearance of vacuolation, and these cells have been termed transitional. The nucleus is round and sharply demarcated by a basophilic outline. It is large, comprising more than half the cell volume. Chromatin usually is abundant.

Occasionally the cytoplasm appears to be entirely absent, *i. e.*, complete vacuolation. This cell is termed "water clear" (wasserhelle). It is sharply outlined and larger than the chief cell. The nucleus is usually more hyperchromatic and eccentrically located. It may occur singly among transitional cells or in groups.

The oxyphil cell is said to appear after puberty, and to increase in number with advancing age, forming large islands which are sharply outlined but not encapsulated. It is polyhedral in shape with a well defined cell margin and is larger than the chief cell. The cytoplasm is uniformly reddish-pink and usually completely fills the cell. The nucleus is about the size of the chief cell but not so hyperchromatic. In this study the cell was seldom seen to occur singly. The islands were usually located subjacent to the capsule or close to the connective tissue stroma. The dark oxyphil cell as described by Castleman and Mallory[17] was not observed. Best Carmine stain was used in some instances to demonstrate glycogen which was found to be present in the chief but not in the oxyphil cells.

In a few areas the acinous nature was so marked that it simulated the structure of the thyroid gland. In some sections thymic tissue was found attached to parathyroid tissue, and cord-like buds of chief cells were seen extending into the lymphoid stroma. The appearance was such that it suggested a close relation might exist at some time between the epithelial cells of the Hassall's corpuscles and the epithelial cells of the parathyroid.

PATHOLOGICAL PHYSIOLOGY. The parathyroid hormone acts chiefly upon the metabolism of calcium and phosphorus and apparently regulates the level of calcium ions. There is some evidence that the stimulus for the parathyroid glands to produce more hormone is a serum calcium ion level below normal.

No unanimity has been reached about the mechanism by which hyperparathyroidism leads to the changes in bone and to the typical biochemical syndrome. Collip and others believe that the hormone has a specific action on bone tissue, causing, notably, proliferation of osteoclasts which in turn lead to resorption of bone and perhaps the formation of giant cell tumors.[31,46] Excessive amounts of calcium and phosphorus are liberated from the skeleton and transported by the blood to the kidneys and intestines. In this way the hypercalcemia, as well as the excessive amount of calcium and phosphorus in the urine can be explained. Why the inorganic phosphorus content of the blood diminishes under the circumstances is not clear.

It is Albright's contention[1,3] that hyperfunction does not act primarily upon the skeleton but first influences the phosphate metabolism. He believes the hormone lowers the renal threshold for the excretion of phosphorus in the urine and thereby increases the phosphorus output. This is attended by fall of the inorganic phosphorus and a rise of calcium in the serum. The urinary calcium first decreases and then increases. The decrease of the phosphate ions in the serum, resulting in unphorus compounds of the blood. The concentration is a measure of disease of bone and not of hyperparathyroidism. Where there is little or no bone involvement its value is normal. In osteitis fibrosa cystica of von Recklinghausen, in which proliferation of osteoblasts and new formation of bone is constantly present, the phosphatase content of the blood is increased.

CLASSIFICATION OF DISEASES OF THE PARATHYROID GLANDS. Clinically significant diseases of the parathyroid glands de-

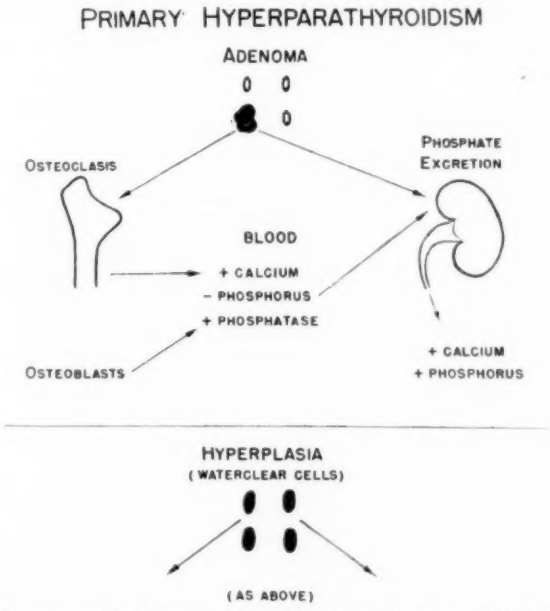


FIG. 3.—Primary hyperparathyroidism. Scheme to show the characteristic biochemical changes when due to an adenoma or to hyperplasia, and the mechanism by which they occur. Collip believes that the hormone has a specific action on the osteoclasts which resorb bone tissue and leads to hypercalcemia. Albright believes that its action is first on phosphate metabolism. The renal threshold for the excretion of phosphorus is lowered, and the effect on calcium metabolism is a sequella.

saturation of the blood with calcium phosphate, ultimately leads to liberation of the calcium phosphate of the bones. The influence of the hormone on calcium metabolism and on the bones would then be only a sequella of the change of phosphorus metabolism. Not all the investigations give confirmatory evidence to this view.

The serum alkaline phosphatase is apparently derived from osteoblastic tissue.[15] It is an enzyme capable of liberating inorganic phosphorus from the organic phospend on whether there is too much or too little of the hormone produced, and may be classified simply under three headings:

1. PRIMARY STATES (other than neoplasms where no cause has been found). From 1934 to 1947, 26 cases of hyperplasia with hyperfunction have been reported.[5,16] In each instance all of the glands were involved and were composed entirely of water clear cells. Chronic idiopathic hypoparathyroidism, in which there is atrophy

of the parenchyma with fat replacement, is equally as uncommon.

2. Secondary States. Physiopathologic conditions resulting in chronic renal insufficiency with phosphate retention and chronic acidosis, and diseases which deplete the available calcium in the body (rickets, osteomalacia, multiple myeloma, carcinomatous metastasis to bones, etc.) can cause hyperplasia of the chief cells with enlargement and hyperfunction of the parathyroid glands as a compensatory measure. Hypofunction, which may result in tetany, will occur when there has been sufficient injury to or excision of parathyroid tissue during thyroidectomy.

3. Neoplasms. In 1902 the first case with reliable evidence of an adenoma was published;[14] reports of cases through 1946[39] have mounted to 337. Usually the tumor involves one gland. However, in about 8% two separate adenomas have been found. In the hyperfunctioning tumors, the chief cells are responsible. Adenomas consisting of oxyphil cells have not been shown to produce hyperparathyroidism. These cells have no known function.

Hyperfunctioning tumors giving unequivocal clinical evidence of malignancy are exceedingly uncommon. In rare instances have they been shown to recur, invade, or metastasize.[9,27,29,30,38] There have been confusing reports of non-functioning malignant parathyroid tumors.

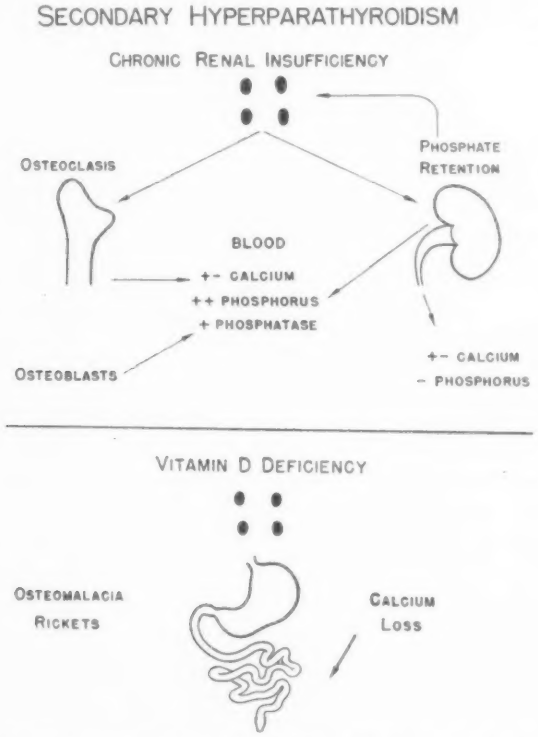


Fig. 4.—Secondary hyperparathyroidism. Scheme to show the biochemical changes and the mechanism by which they occur. In chronic renal insufficiency the stimulus to overactivity of the gland apparently results from phosphate retention. In osteomalacia and rickets, the stimulus is a calcium deficit in the blood stream.

Clinical Manifestations of Hyperparathyroidism. The clinical manifestations of hyperparathyroidism are protean and most variable. The way in which the disease becomes evident may be shown by

its effect upon the circulating blood, the urinary tract, and the skeleton.

1. Blood (increased calcium—decreased neuromuscular excitability): Apathy, weakness, fatigue, anorexia, nausea and vomiting, constipation, weight loss, bradycardia, cardiac irregularities, and conduction defects.

2. Urinary Tract: Increased calcium and phosphorus excretion attended by thirst and increased urine output; renal calculi with resultant symptoms; and renal damage from calcium deposits in the parenchyma, pyelonephritis or obstruction with evidences of insufficiency.

3. Skeleton (demineralization and osteoclasis): Pain and tenderness of bone, pain on weight bearing, pathological fractures, deformities, decrease in height, cysts, tumors, epulides.

The full range of symptoms is to be encountered only in a case of severe "classic" osteitis fibrosa cystica, and even then there is marked variation in their occurrence and severity. In most cases the history has disclosed that the patient has had the disease years before the diagnosis was made.

Except in instances of severe hypercalcemia, symptoms may be vague, and in cases in which there is minimal alteration of the chemistry of the blood they are often absent. Since the chemical alterations are the reverse of those encountered in parathyroid tetany, one would expect to encounter symptoms which represent the converse of tetany, *i. e.*, decreased neuromuscular irritability. This is, indeed, the case. Occasionally, gastrointestinal symptoms, such as attacks of abdominal pain, nausea and vomiting, are the predominant features.

The excessive loss of minerals is accompanied in most instances by conspicuous polyuria and polydypsia which has led to a mistaken diagnosis of diabetes insipidus. Polyuria is not always present and its presence or absence cannot be correlated with the degree of calciuria which exists.

In a high percentage of cases, symptoms associated with nephrolithiasis are the first manifestations of the disease. Calcium salts may be deposited also in the pyramids (nephrocalcinosis) and lead to renal insufficiency. The diffuse calcification of the renal parenchyma, associated with fibrosis and destruction of renal substance, leads to irreversible changes even though the hyperparathyroidism is eliminated. It may be difficult to distinguish clinically primary hyperparathyroidism with osteitis fibrosa cystica and secondary urinary insufficiency, from primary renal disease with accompanying secondary hyperparathyroidism and renal osteitis fibrosa cystica. The distinction is important, for, in the case of primary disease, removal of the parathyroid tumor may prolong life, whereas it is probable that, in primary renal disease with secondary hyperparathyroidism, parathyroidectomy would shorten life.

In many cases in which the absorption of calcium from the diet is approximately equal to that lost through the urine, no evident change occurs in the skeleton. In other cases, there may be any degree of skeletal involvement. Patients with minimal changes may have no symptoms whatever, or, at the most, have vague aching and pain. When involvement is more marked, pain and tenderness of bones and especially pain on weight bearing are presenting symptoms. Any bone tumor which on biopsy turns out to be a benign giant cell tumor (osteoclastoma) may be evidence of underlying hyperparathyroidism. Such a tumor of the jaw is called an epulis; it is present in an appreciable number of cases, and might direct the attention to the underlying disease. Not every epulis, however, is due to hyperparathyroidism. A pathological fracture sometimes is the first clue to the disease.

The differential diagnosis has consisted largely in distinguishing hyperparathyroidism from other conditions which produce hypercalcemia and from diseases affecting the skeleton in a similar manner. Essential laboratory data in arriving at the diagnosis in a given case should in-

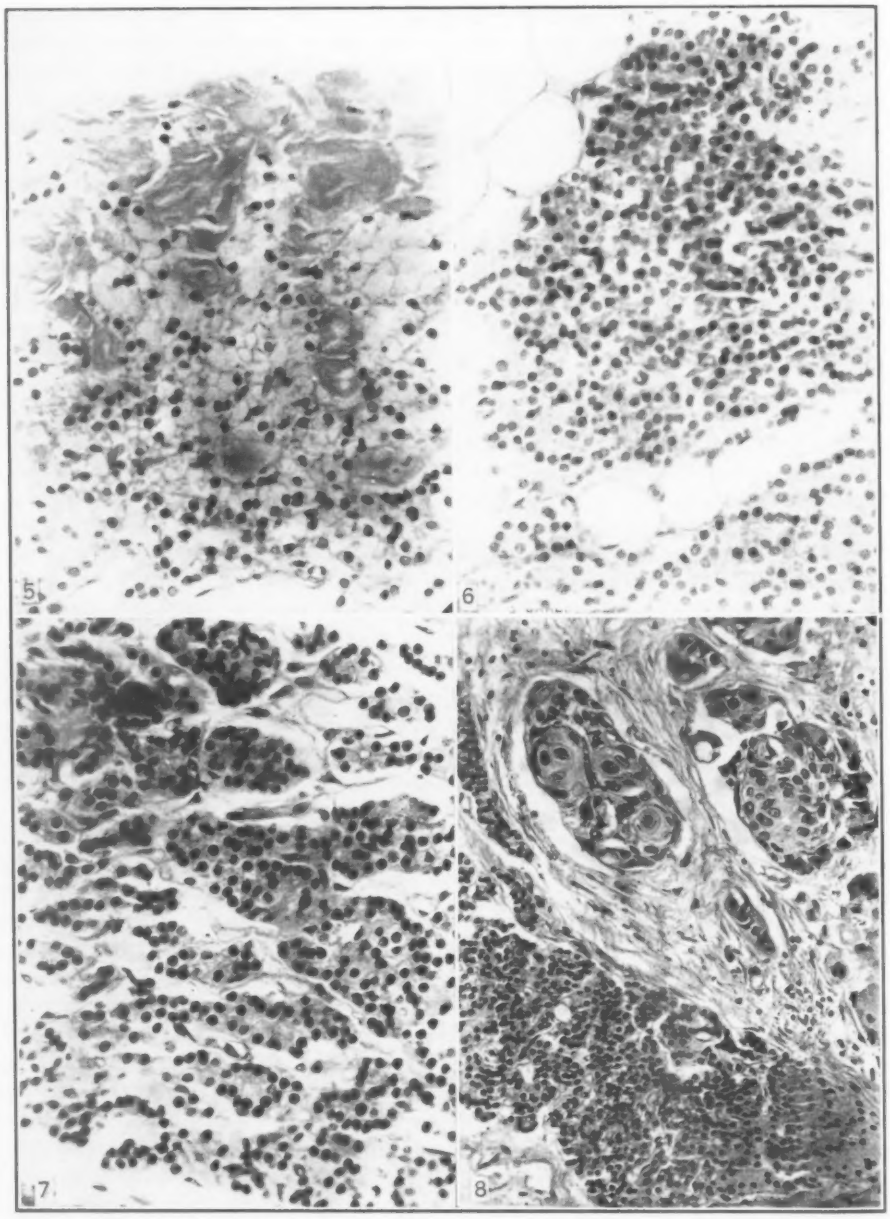


FIG. 5.—The parathyroid gland from a patient (CASE 1) with severe chronic arthritis deformans. Water-clear cells and hyaline degenerative changes are seen. (× 350.)

FIG. 6.—The unirradiated left parathyroid gland (CASE 2). Fat cells are seen in the stroma. (× 350.)

FIG. 7.—The irradiated right parathyroid gland (CASE 2). The chief cells are shrunken and their nuclei tend to be hyperchromatic. Fat cells are absent. There is fibrosis about the cords. (× 400.)

FIG. 8.—The irradiated right parathyroid gland (CASE 2). Nests of epidermoid carcinomatous cells are seen in lymphatic channels. (× 250.)

clude: repeated determinations of serum calcium and phosphorus, serum proteins, non-protein nitrogen, carbon dioxide combining power, and serum alkaline phosphatase when there are bone changes.

Histopathology. CASE 1. Degenerate parathyroid gland showing only water clear cells.

In Figure 5 is shown the histopathological findings in the parathyroid removed from a patient (J. C.), age 50 years, who for 9 years had been unable to walk because of severe arthritis deformans involving all major joints. He had been cared for in the Veterans Hospital for 8½ years before death and was found also to have renal calculi with evidence of kidney damage. Roentgenographs of the bones disclosed generalized osteoporosis. Serum calcium and phosphorus levels were within normal limits. The serum alkaline phosphatase was elevated. The N.P.N. rose from 35 to 100 mg. during the last year of life.

At necropsy, the kidneys were found to be badly damaged. Only one pale yellow parathyroid gland, of normal size, was found. It consisted entirely of water clear cells with scattered fat cells. There were marked hyaline degenerative changes in the subcapsular region, between the lobules, and around the arterioles.

CASE 2. Effects of irradiation therapy and metastasis of carcinoma to right parathyroid.

In the case of A. J., the effects of irradiation on the parathyroid gland can be seen (Figs. 6, 7, 8). The patient was a 62 year old male who was admitted to the hospital for treatment of bronchogenic carcinoma with cervical metastasis. He was given palliative irradiation over a period of 1 month, consisting of 1950 R units to each the anterior and posterior mediastinum and 3000 R units to the right side of the neck. The left side of the neck was not irradiated. Postmortem examination showed the right lobe of the thyroid to be replaced by carcinoma. A soft, pale tan parathyroid gland, 6 x 2 x 2 mm., was on the anterolateral surface of the metastatic tumor mass to which it was loosely attached. The left lobe of the thyroid was uninvolved, except for a metastatic nodule in the lower pole. A normal-sized parathyroid gland with slightly darker color was located just below the left inferior pole.

Histologically, the left parathyroid gland showed a predominance of chief cells. There were several acini, two of which were moderately large and contained colloid-like material. Two small islands of oxyphil cells were present and fat cells were scattered throughout. The right gland (irradiated) showed shrunken chief cells with increased fibrosis about the cords. There were no oxyphil or fat cells. Nests of epidermoid carcinomatous cells were present under the capsule and in the lymphatic channels.

CASE 3. Minute oxyphil adenoma.

The photomicrograph shown in Figure 9 was made from a patient (A. H.), age 57 years, who died from a brain tumor. A review of the clinical studies disclosed no evidence suggesting hyperparathyroidism. Serum calcium and phosphorus were not determined.

The parathyroid glands grossly appeared normal. However, one gland disclosed on section a well circumscribed adenoma (1½ x 1 mm.), consisting of pale oxyphil cells. Some of these cells contained vacuoles and one small acinus with colloid material in it was noted. The surrounding chief cells were compressed and arranged in cords.

CASE 4. Hyperfunctioning parathyroid adenoma; report in detail.

W. J. U., a white Spanish American War veteran, age 70 years, was admitted to the Veterans Hospital, Hines, Ill., May 28, 1946, for the treatment of "probable carcinoma of the descending colon." He died 3 months later.

History. Members of the family lived to be old. There was no record of cancer. The patient had received radium pack treatment to the thyroid area for goiter.

The patient first noticed a change in the shape of his chest about 1939, at which time he began to experience indefinite aches and pains. He had begun to lose weight, having weighed over 200 pounds at one time, became weakened, and noticed that his height was diminishing (maximum height was 71 inches, present height 65 inches). Symptoms of frequency and urgency of urination followed, and about 1940 a suprapubic prostatectomy was performed. He was told that no growth was found.

Two years before admission he tripped on a rug and fractured the left hip and left

humerus. The humerus was impacted and required no immobilization. The femur was treated by insertion of a Smith-Petersen pin. The family was told that the bone was abnormally spongy. Following this he was up and about with the aid of crutches.

About 6 months before admission he developed a diffuse itching of the skin which persisted. Two months before admission he had a painful pruritic eruption of the right side of the back which was diagnosed shingles. The day prior to hospitalization he began to have sharp sticking pains in the left lower quadrant when he moved his body and when he urinated.

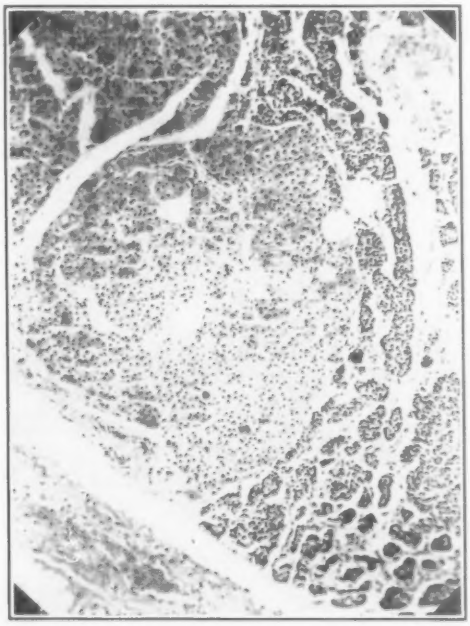


FIG. 9.—Part of a minute oxyphil cell adenoma (CASE 3). It is well circumscribed and the surrounding chief cells are arranged in cords and appear compressed. (× 150.)

Gastrointestinal tract: Appetite had been finicky for the past 3 months. There were frequent episodes of constipation but no diarrhea. He had vomited after breakfast for the past 10 days. Cardiorespiratory tract: Essentially negative. Genito-urinary tract: Nocturia 3 times nightly. No hematuria and no history of renal colic.

Physical Examination. A poorly nourished bedridden white male who appeared chronically ill and older than his 70 years. There were deformities of the chest (lateral narrowing), left hip, left shoulder, and joints of the fingers. The left leg was 1 inch shorter than the right. Movement of the left leg caused pain in the lower abdomen. The back showed a marked thoracic kyphosis with slight scoliosis.

The head was of normal configuration. The eyes were essentially normal except for impaired vision, band-shaped keratitis bilaterally, and right senile entropion. Hearing was impaired. The oropharynx was negative. The patient was edentulous. The lobes of the thyroid gland were enlarged and nodular.

Expansion of the chest was limited considerably. Lung fields were clear. The heart was not enlarged. Sounds were distant. Blood pressure 130/80. The abdomen was soft and no masses were palpable. There was tenderness in the left lower quadrant. A midline surgical scar was present below the umbilicus. Rectal examination disclosed no masses. The prostate was normal. The genitalia was normal.

The skin was pale, dry, and thin. Scars of herpes zoster were present along the right upper chest wall. Small, shotty lymph nodes were palpated in the neck, axillæ, and groins. The reflexes were active and equal. There were no pathological responses.

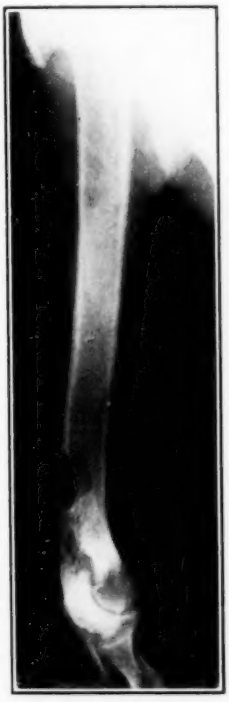


FIG. 10.—Roentgenogram of left humerus shows osteoporosis and a cystic area. There is evidence of a healed fracture of the surgical neck. (CASE 4.)

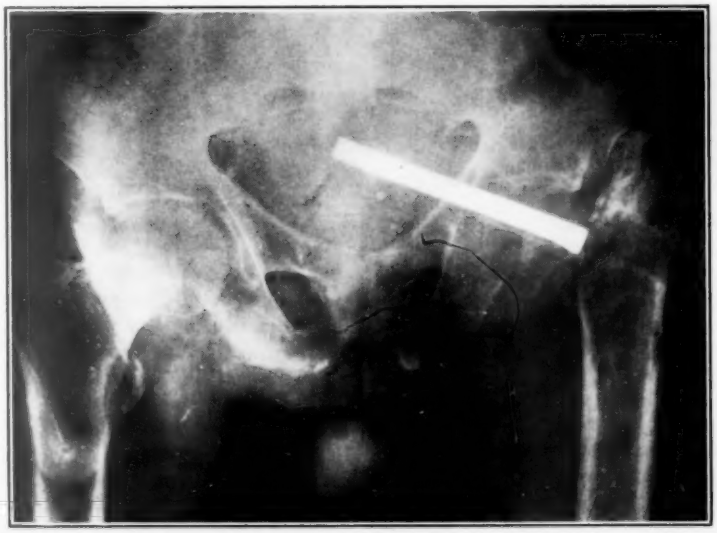


FIG. 11.—Roentgenogram of pelvis shows the migrating Smith-Petersen pin extending through the left acetabulum. There is an old unreduced fracture of the neck of the left femur. Osteoporosis and cystic changes are present. (CASE 4.)

Special Examinations and Laboratory Data. Roentgenographic studies (Figs. 10, 11, 12) showed generalized osteoporosis of the long bones and numerous cystic areas. There appeared to be some increase in thickness and density of the bones of the cranial vault. Evidence of a healed fracture of the surgical neck of the left humerus was present. There was an old unreduced fracture of the anatomical neck of the left femur. A migrating Smith-Petersen pin was seen extending through the acetabulum into the pelvis. A barium enema was negative. Electrocardiograms were abnormal, showing atrioventricular block and evidence of myocardial damage. Cystoscopic examination showed a trigonitis and elevation of the trigone on the left due apparently to external pressure by the Smith-Petersen pin.

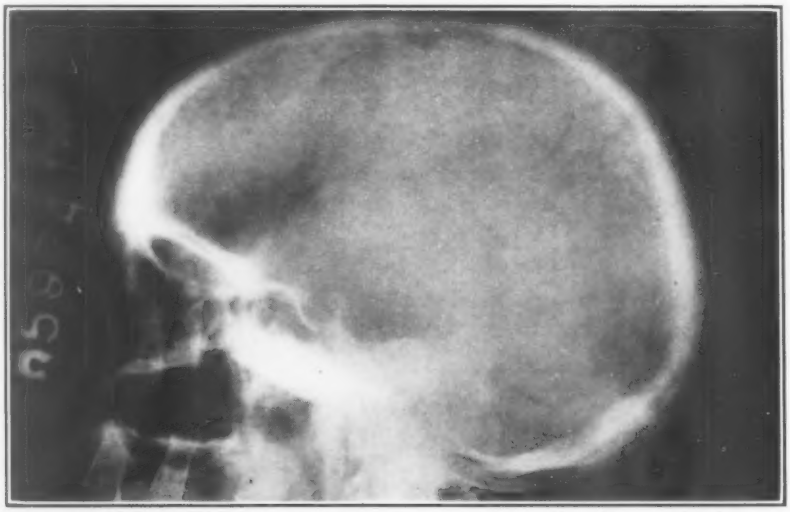


FIG. 12.—Roentgenogram of skull shows some increase in thickness and density of the bones of the cranial vault. This roentgenological finding was largely responsible for the early impression that the patient had Paget's disease of the bone. (CASE 4.)

A moderate anemia was present. The initial blood count was: Hemoglobin 10 gm.; RBC, 3,250,000; WBC, 9,200 (neutrophils 92%; lymphocytes 8%). Urinalyses showed traces of albumin with moderate to many WBC, few RBC, and no casts. Specific gravities ranged between 1.003 and 1.012. P.S.P. showed 10% excretion of the dye at the end of the first hour and 10% at the end of the second hour. Sixteen N.P.N. readings ranged between 49 and 200 mg. Six serum calcium determinations ranged between 14 and 19.5 mg. Seven serum phosphorus determinations ranged between 3.4 and 4.4. Urinary calcium excretion determinations showed increased 24-hour output. The alkaline phosphatase was slightly elevated (4.5 and 6.8 Bodansky Units). The serum proteins were 6.9 mg. with normal albumin-globulin ratio. Bence-Jones protein was negative.

The first impression was that the patient had Paget's disease of bone and it had been proposed to remove the migrating Smith-Petersen pin. However, during the time that effort was being made to improve his general condition and the uremic state it became apparent through further studies of the blood chemistry that the true diagnosis was osteitis fibrosa cystica generalisata (von Recklinghausen's disease), secondary to a parathyroid adenoma.

Preoperatively the patient was restless and averse to eating. He complained of dryness of the mouth, itching of the skin, and occasionally vomiting. Cheyne-Stokes respiration was present at times. On June 19, 1946, a weakness of the left arm was noted. He developed a fecal impaction, following which he had diarrheal stools for several days. Although there was apparent improvement in the uremic state, his general condition

did not improve. At the onset he was able to be out of bed in a wheel chair for an hour, but later he could not be encouraged to get up at all. The pulse rate varied between 100 and 120 per minute and there were occasional extra systoles. Urinary output was within the normal amount.

Postoperative Course. On the day of operation the patient was given 20 cc. of 10% calcium gluconate (2 gm.) intravenously and 2 cc. (20 units) of parathyroid extract intramuscularly. On the following day he received with intravenous fluids 40 cc. of 10% calcium gluconate (4 gm.), and 20

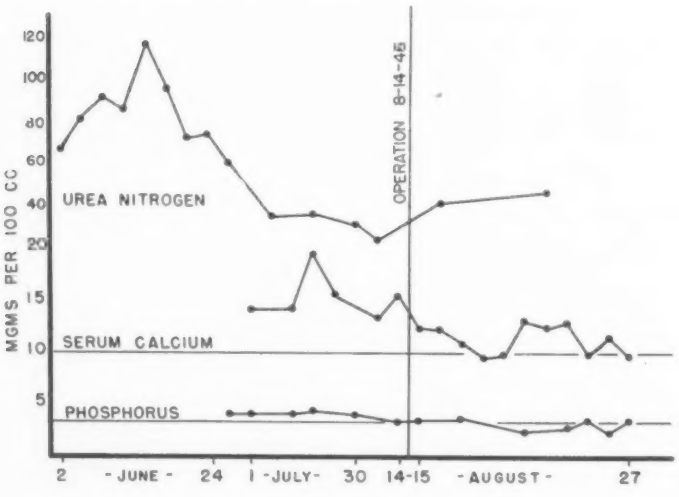
FIG. 13.—Thyroid gland and parathyroid adenoma (surgical specimen). The thyroid is enlarged and nodular. The tumor (sectioned) at the right lower pole of the thyroid weighed 10 gm. and measured 3½ x 3½ x 2 cm. The cyst can be seen. (CASE 4.)

Operation. On August 14, 1946, under endotracheal general anesthesia, exploration of the neck was done. The thyroid was enlarged and adenomatous with degenerative changes throughout consisting of small cysts and calcified areas. At the lateral border of the right lower pole posteriorly, in the tracheo-esophageal groove, was a grayish-yellow, soft, lobulated tumor which contained a cystic area ¾ cm. in diameter, with a partially calcified wall and a calcified nodule ½ cm. in diameter in the center (Fig. 13). The tumor was distinctly paler and softer than the thyroid lobe to which it was attached by connective tissue. It measured 3½ x 3½ x 2 cm. and weighed 10 gm. The other parathyroid glands were not seen. The tumor and most of the thyroid gland were removed.

units of parathyroid extract intramuscularly. Dihydrotachysterol ½ cc. was given orally that evening. Daily thereafter he was given ½ cc. of dihydrotachysterol until August 25, 1946 (eleventh postoperative day), at which time he refused to take some of his oral medications and it was not thought necessary to continue it.

The blood chemistry findings, including urea nitrogen, calcium, and phosphorus, are shown in Figure 14. Postoperatively the serum calcium was seen to fall to normal by the fourth day and then to rise again. The possibility of another parathyroid adenoma was considered.

On the first postoperative day the urinary output measured 850 cc. The patient did not develop an oliguria although he had difficulty in voiding and required catheteriza-



GRAPH SHOWING PRE- AND POSTOPERATIVE BLOOD CHEMISTRY FINDINGS

FIG. 14.—Preoperative and postoperative chemical findings. Preoperatively, there was improvement in the uremic state. Repeated serum calcium values were elevated. Serum phosphorus values were within normal range, presumably because of the renal damage.

Postoperatively, on the day of surgery and the first day after surgery, he was given calcium gluconate and parathyroid extract. Subsequently he took, orally, ½ cc. of dihydrotachysterol each day until the eleventh postoperative day. The serum calcium is seen to fall to normal by the fourth day and then to rise again. Because of this, the possibility of another parathyroid adenoma was considered. (CASE 4.)

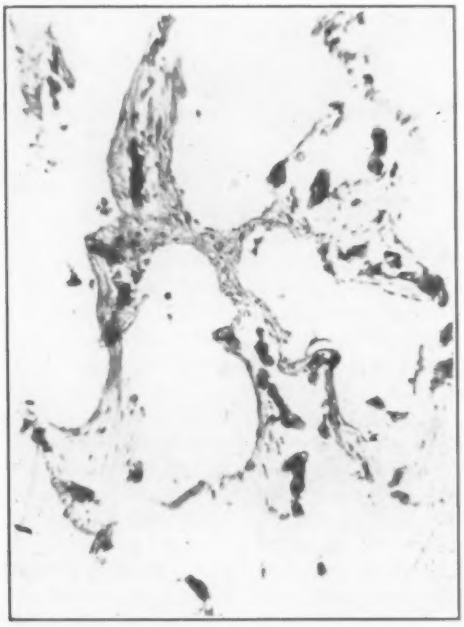


FIG. 15.—Lung. Calcium deposits are seen in the alveolar septa; there is much connective tissue reaction. (CASE 4. × 300.)

tion. He remained apathetic and at times was noisy and confused. He had difficulty in raising accumulations of mucus from the throat, and nose and throat examination showed that he had developed paresis of the inferior laryngeal constrictor muscles. Electrocardiograms disclosed an auricular fibrillation. It became difficult for him to swallow food or liquids and at times respirations came slow and labored. Considering his poor condition preoperatively, the postoperative state was not thought alarming until August 29 (fifteenth postoperative day) when he suddenly became dyspneic and expired within a few minutes.

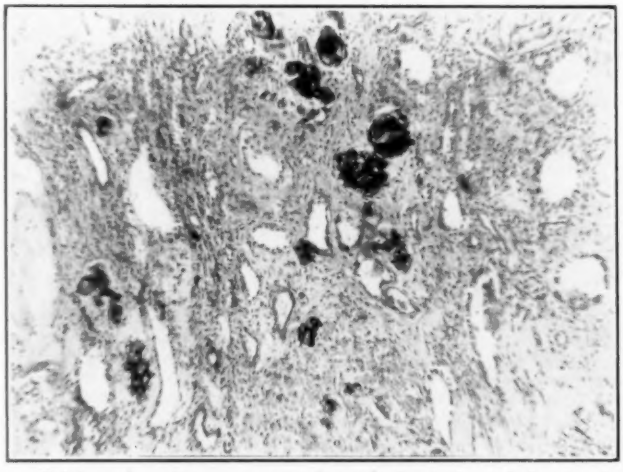


FIG. 16.—Kidney. Calcium deposits are present in and about the tubules (nephrocalcinosis) with reactive fibrosis. (CASE 4. × 150.)

Necropsy. The surgical neck wound was well healed. There was a decubitus over the midthoracic vertebræ. Body weight was about 98 pounds. Careful search for parathyroid tissue was made in the neck and in the anterior and posterior mediastinum, taking many specimens for histological study. None was found. Only about ½ gm. of thyroid tissue remained at the right upper pole. There were no significant findings in the heart and lungs. The aorta showed severe arteriosclerosis. The gastrointestinal tract was negative. A calculus 1 cm. in diameter was present in the gallbladder. The kidneys were markedly contracted and had coarsely granular surfaces; each weighed 50 gm. Cut section showed several cysts with thick, partially calcified walls. Gritty, yellow granules were present throughout the parenchyma, especially about the cysts. Division between cortex and medulla was indistinct. No calculi were present in the rest of the urinary tract. The urinary bladder and ureters were grossly normal. There was no obstruction to the bladder neck. The prostate was small. The Smith-Petersen pin had migrated a distance into the pelvis 4 cm. from the left acetabulum to the left side of the sacral promontory. It was covered only by peritoneum. The bony skeleton showed a soft round area, 1½ cm. in diameter, in the left parietal bone of the skull. A hard nodular area was observed in one rib. The bone of the left clavicle and lumbar vertebræ showed no gross change.

Significant Histopathological Findings. There were calcium deposits in the alveolar septa of the lungs with fibrous reaction (Fig. 15). Calcium was also present in considerable amounts in the parenchyma of the kidneys (Fig. 16). There was much associated reactionary fibrosis and the glomeruli were badly damaged, many of which were hyalinized and fibrosed. There was mild hyperplasia of the prostate. Some sections of the bone showed proliferation of fibrous tissue with thinning of the trabeculæ. Most sections were not unusual, however. There was considerable fibrosis in the spleen. No evidence of calcification was seen in sections from the gastrointestinal tract. The brain disclosed moderate gliosis. The small

vessels were thrombosed and there was some degeneration of the nerve cells, showing pigmentation. There was calcification in the media of the small arteries in sections taken from the neck.

Histological examination of the parathyroid adenoma showed it to be composed largely of chief cells with islands of pale oxyphil cells present here and there. There was considerable dense connective tissue running in bands which had divided the tumor into lobulations. Various cell patterns were present, including areas of many small follicles, arrangement of cells in cords, and arrangement of cells in broad sheets, the latter being most common (Fig. 17). There were calcified areas, one large cyst, a very vascular area, and an area with marked hyaline changes among the cells. In some sections the cells varied considerably in size and shape. In most sections the cytoplasm stained uniformly but there were a few areas in which there was vacuolation. The nuclei also varied in size and shape and in intensity of staining. The cells were especially distorted in the dense connective tissue and calcified zones. Few mitotic figures were present. There was no evidence of invasive tendency.

Best Carmine stain disclosed fine glycogen granules in the cytoplasm of the chief cells but not in appreciable amount in most areas. Special staining (Sudan IV) showed no fat in the tumor cells.

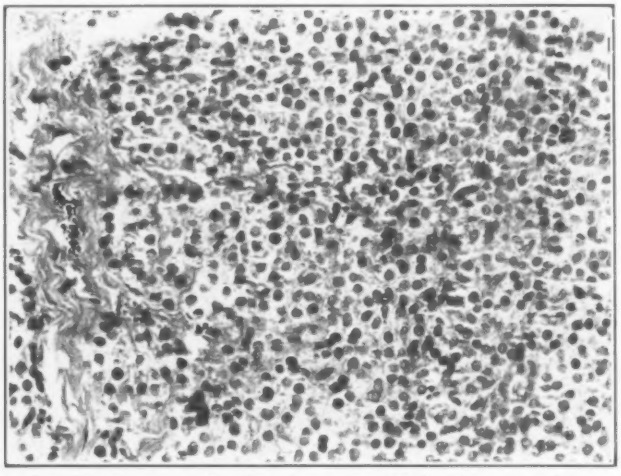


FIG. 17.—The parathyroid adenoma. Section shows the chief cells arranged in a continuous mass. A dense connective tissue septum is seen on one side. (CASE 4. × 400.)

Summary. A study of the parathyroid gland, based, in part, on 60 postmortem examinations, has been presented. It includes a review of the embryology, anatomy, and histology. Consideration is given to the mechanism of hyperparathyroidism and its clinical manifestations. Certain histopathological features are discussed. A case of osteitis fibrosa cystica generalisata (von Recklinghausen's disease) associated with parathyroid adenoma, including necropsy findings, is reported.

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THE OCCURRENCE OF GASTRIC NEOPLASMS IN YOUTH*

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Gastric carcinoma in individuals 30 years of age and younger is a rare disease. In 1941 McNeer[3] reviewed the world literature on this subject and found 501 cases below the age of 31 and in which the diagnosis was reasonably justified. In addition, he reported 5 cases of his own, collected from a total series of 682 cases of gastric cancer, an incidence of 0.7%. In the earlier literature Welch[6] reported an incidence of 2.8% of gastric carcinoma in this age group of a total of 2038 cases. More recently, Walters and his co-workers[4] collected 24 instances of gastric carcinoma between the ages of 24 and 29 from a total of 2772 resected cases. By considering all cases of carcinoma of the stomach, Walters, Gray and Priestley[5] reported the largest single series of carcinoma in youth. Of a total of 10,890 cases there were 90 below the age of 30 with carcinoma of the stomach. The youngest case in this series was a male aged 18.

Because of the rarity of this condition in youth, there has been a frequent tendency either to overlook this diagnosis when the patient is 30 or younger, or if there is clinical and roentgenologic evidence of a gastric lesion to consider other diagnostic possibilities to be more likely. Benign gastric ulcer, gastric lues or gastric lymphoblastoma is usually considered to be the more probable diagnosis, in view of the patient's age. As McNeer[3] pointed out in his review, the roentgenologic evidence of carcinoma is ignored or not considered seriously because of the age of the patient. As a result of this tendency various forms of therapy are resorted to, often for many months before surgical intervention is undertaken. Because of this delay in treatment the prognosis of gastric carcinoma in youth is often permitted to become worse than for older age groups.

Since the primary obstacle in making the diagnosis of carcinoma of the stomach in youth appears to be the patient's age, an effort was made to discover from the literature what the statistical possibilities are that any gastric lesion occurring below the age of 31 is a carcinoma. There is very little evidence on this subject and one is surprised to find that there has been no parallel evaluation of the incidence of benign gastric ulcer and gastric carcinoma in youth (below the age of 31) in any large series of patients. Comfort and Butsch[1] found that benign gastric ulcer in the third decade of life was 20 times more prevalent than was cancer. However, their figures were based on a small group of resected cases in which the lesion was 4.4 cm. in diameter or less, and, as the authors point out, the figures do not represent the actual total incidence of either of the 2 diseases. Likewise, there has been no parallel study of the incidence of other gastric lesions such as lymphoblastoma, benign gastric tumors and gastric lues with gastric carcinoma in youth in any large series of patients. As a result of our failure to find any such parallel data in the literature on either the incidence of benign gastric ulcer or other gastric lesions,

such as lymphoblastoma and lues, in comparison with gastric carcinoma in youth, we felt that the usual clinical dictum that a gastric lesion in a patient below the age of 31 is probably benign was not necessarily justified.

In order to study this problem, a survey was made of the total incidence of gastric carcinoma at the University Hospital during a 20-year period (July 1, 1925 to June 30, 1945). During this period there were 453,400 registrations and during the same period 1913 instances of carcinoma of the stomach (an incidence of 0.42%), which means that in this institution 1 out of every 225 patients registering here has a carcinoma of the stomach. In Figure 1 the age and sex distribution for all cases of carcinoma of the stomach are indicated. This general age and sex distribution is in

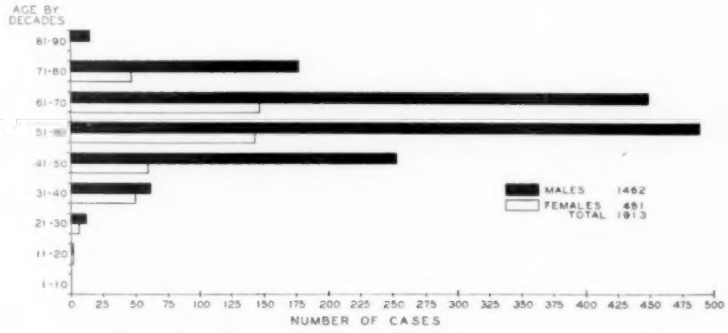

FIG. 1.—Incidence of carcinoma of the stomach during 20 year period by sex and age (July 1, 1925 to June 30, 1945).

close agreement with previously reported surveys.[2,5] Two points in these data seem to us of considerable interest. First of all, there is an absence of any case of carcinoma of the stomach in any female patient over the age of 80. The second point, and more pertinent to our present study is the occurrence of 20 instances of carcinoma of the stomach in patients below the age of 31. This is an incidence of 1.04% of 1913 gastric carcinomas. This figure is in general agreement with the 0.7% incidence reported by McNeer[3] and the incidence of 0.8% of Walters *et al.*[5]

Since our primary interest was in the younger age group a detailed study was made of these 20 instances of carcinoma of the stomach. Table 1 shows the age and sex distribution for this group. Our youngest case was 16 years old, with 13 cases occurring at 25 years of age or older. There were 13 males to 17 females, or roughly 2 to 1. Figure 2 indicates the frequency of symptoms in all 20 cases. Of particular significance was the fact that gastric distress or pain was a prominent and important symptom in 17 cases. Although this epigastric discomfort was usually somewhat different from that occurring in benign gastric ulcer, nevertheless, its frequent occurrence as a promi-

TABLE 1.—AGE AND SEX DISTRIBUTION OF 20 CASES OF CARCINOMA OF THE STOMACH IN YOUTH

Age	Number M	Number F
16	1	
18	..	1
21	..	1
22	2	
23	1	
24	..	1
25	..	1
26	2	
27	2	
28	..	2
29	2	
30	3	1
Total	13	7

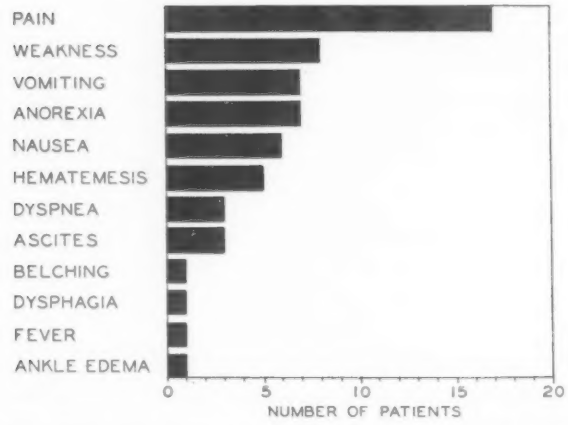

FIG. 2.—Symptomatology in 20 cases of carcinoma of the stomach below age of 31.

nent symptom discouraged the clinical suspicion or diagnosis of neoplasm. The frequency of hematemesis (5 instances) had the same clinical significance, particularly in view of the fact that in 3 instances hematemesis was the initial symptom. Other pertinent data in the entire series are graphically represented in Figure 3. These data are those obtained at the time of the original examination at the Uni-

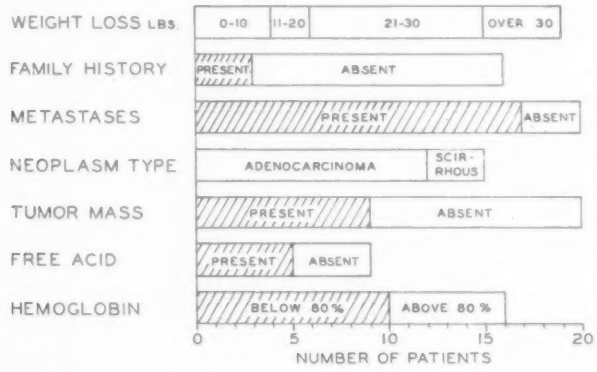

FIG. 3.—Pertinent data on 20 patients 30 years old and below with carcinoma of the stomach.

versity Hospital and generally reveals the fact that at this time the disease was far-advanced. In 9 instances (45%) there was a palpable tumor mass, and in 17 cases (85%) metastases were demonstrable either clinically or at the time of operation. In fact, metastases were so marked that definitive surgical therapy was considered feasible and carried out in only 3 cases. Fifteen other cases were subjected to an exploratory laparotomy and metastases confirmed. In 2 instances metastases were demonstrable by lymph node biopsy. In 5 of the 9 cases subjected to gastric analysis free acid was present. Weight loss was significant in 16 instances and definite anemia was present in 10 cases. Of great interest was the occurrence of a family history of gastric neoplasm in only 3 patients (15%). This figure does not differ greatly from the incidence of 20% reported by Walters.[5]

The delay in diagnosis and course of the disease after the diagnosis was established is indicated in Figure 4. Of great significance is the fact that in 5 cases (25%) the diagnosis was not established until 19 to

24 months after the onset of symptoms. Actually, in all 5 cases included in the 19to 24 month period, the diagnosis was established at the upper limit of this period, 24 months after onset of symptoms. The average time for diagnosis after onset of symptoms for all cases was 11.5 months. The time of death was known only in 14 cases and the average duration of life after the onset of the initial symptoms in this

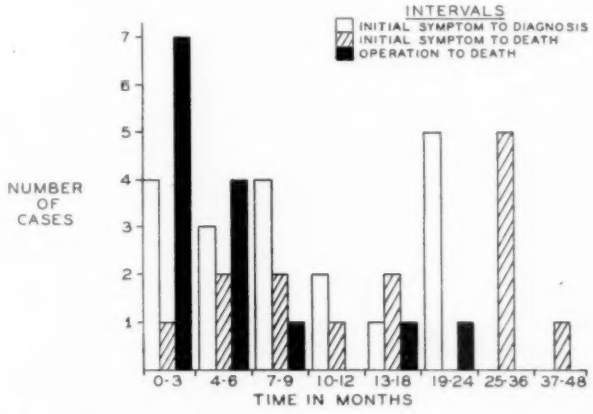

FIG. 4.—Diagnostic and prognostic intervals in 20 cases of carcinoma of the stomach in youth.

group was 17.4 months. In 1 instance death occurred within 3 months (Figure 4). The duration (average 5.3 months) of life after operation is not a criterion of the efficacy of surgical treatment in our series, since as previously indicated, metastases were present in 85% at the time the patient was first examined. In the 3 instances where definitive surgery was considered feasible and carried out, the postoperative duration of life was 5, 15, and 23 months respectively.

The delay in diagnosis in most cases was associated with two facts: (1) The failure of the patient to consult a physician early after the onset of symptoms and (2) the fact that because of the patient's age, there was a tendency on the part of the physician not to diagnose neoplasm in spite of suggestive and even definite clinical and roentgenologic findings. Benign gastric ulcer was nearly uniformly considered a more likely diagnosis. In 8 of our 20 cases it

TABLE 2.—DATA OF PATIENTS WITH INITIAL DIAGNOSIS OF PEPTIC ULCER

Case No.	Clinical story	Initial Roentgen ray findings	Intervals from operation to death
1	Recurrent gastric distress for 10 years. Treated intermittently for ulcer.	Negative	1 month
2	Ulcer-like symptoms for 5 years. Diagnosis of peptic ulcer.	Diagnostic of neoplasm	2 weeks
3	Epigastric distress for 2 years. Treated for ulcer.	Negative	5 months
4	Diagnosis of gastric ulcer. Treated for 33 months.	Gastric ulcer, regression, then recurrence	9 months
5	Diagnosis of aerophagia 6 years prior to discovery of neoplasm. Ulcer diagnosed 4 years later. Relief by diet.	Diagnostic of neoplasm	23 months
6	Epigastric distress for 2 years. Treated for peptic ulcer.	Diagnostic of neoplasm	2 months
7	Abdominal discomfort and cramping for 5 years. Treated for ulcer	Gastric ulcer	Exact time of death unknown
8	Five year history of ulcer type of distress.	Diagnostic of neoplasm	5 months

was possible to demonstrate that the patient had consulted a physician soon after the onset of symptoms, but a diagnosis of gastric ulcer was made and the patient treated medically. Data on these 8 cases is summarized in Table 2. The initial Roentgen ray findings at the University Hospital are indicated and it is of interest that 2 were negative, 2 were considered diagnostic of benign gastric ulcers and 4 were diagnostic of gastric neoplasm. Case 4 is of particular interest in that the original diagnosis was benign gastric ulcer March 8, 1938 (Figure 5). Partial healing seemed apparent on Roentgen ray within 3 weeks. This partial healing was accepted

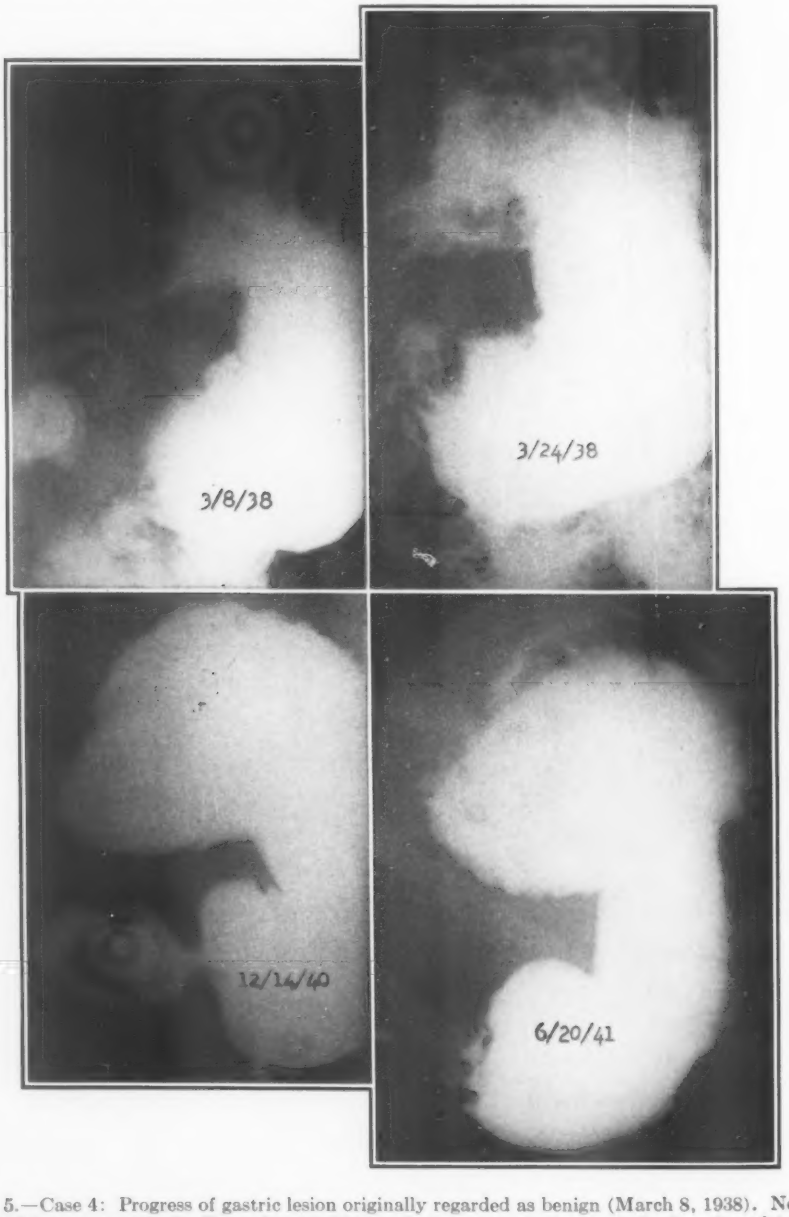

FIG. 5.—Case 4: Progress of gastric lesion originally regarded as benign (March 8, 1938). Neoplasm suggested by roentgenologist December 14, 1940 and metastases (supraclavicular lymph node) demonstrated June 20, 1941.

as definite evidence of benignity of the lesion and there was no further follow-up until recurrence of symptoms in December, 1940. At this time (Dec. 12, 1940) the roentgenologist first suggested the diagnosis of gastric neoplasm. In view of the patient's age the clinician ignored this suggestion and continued medical therapy until June 20, 1941, when definite metastasis was present. Death occurred 9 months later. It is not pertinent to this report to discuss whether or not this was an instance of malignant degeneration of a benign ulcer or whether this ulcer was throughout its course a malignant ulcer. However, two points are worthy of emphasis. First, because of the false security that the patient's age gave the clinician, the patient was not followed as closely as indicated. Secondly, because of the patient's age the occurrence of a gastric ulcer which did not remain healed did not appear to be an indication for surgical intervention as would have been the case in an older patient.

In view of this general tendency to consider that gastric lesions in youth are more likely to be benign than malignant, a survey was made of all gastric lesions that had occurred in individuals below the age of 31 during the same 20-year-period. Results are shown in Figure 6. There was a total of 73 gastric lesions in this age group. Fifty of these were benign ulcers, 20 were

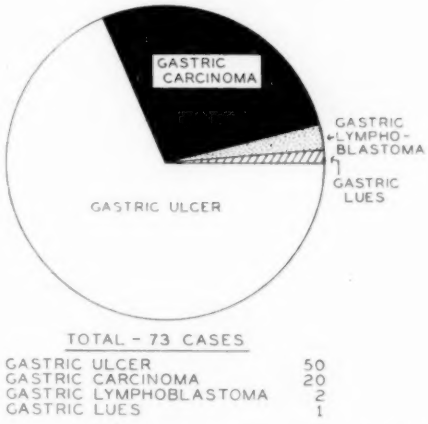

FIG. 6.—Incidence of all gastric lesions in patients under 31 years of age during 20 year period.

carcinomas, 2 were lymphoblastomas and 1 was gastric lues. This indicates that in this age group, although gastric lesions are rare, when one does occur there is approximately a 30% chance that it is a carcinoma. If one includes the 2 cases of primary gastric lymphoblastoma, the chances that a gastric lesion occurring below the age of 31 is neoplastic are even more impressive.

Summary and Conclusions. 1. A survey of the occurrence of carcinoma of the stomach during a 20 year period (July 1, 1925, to June 30, 1945), at the University Hospital revealed that there were 1913 carcinomas out of a total of 453,400 registrations. This is an incidence of 0.42%.

2. Of the 1913 carcinomas during this same period, 20 (1+%) occurred in patients below the age of 31. Of these 20 cases, 17 had metastases when first examined, and the diagnosis of carcinoma was usually delayed because benign gastric ulcer was generally considered the more likely diagnosis in view of the patient's age.

3. During the same 20 year period 53 other gastric lesions (50 benign gastric ulcers, 2 gastric lymphoblastomas, 1 gastric lues) occurred in the same age group.

4. These figures demonstrate that all gastric lesions are rare in patients below the age of 31, but once a gastric lesion does occur the probability that it is neoplastic is at least 30%.

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PLASMOCYTOMA (MULTIPLE MYELOMAS, KAHLER'S DISEASE), AND ITS ATTENDANT DISTURBANCES IN THE PROTEIN METABOLISM

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INTERNIST AT ZWOLLE, HOLLAND

I. *All multiple myelomas are plasmocytomas.* In the Netherlands Medical Journals articles dealing with the above-mentioned subjects have repeatedly appeared during the last few years. None of the authors of these articles, however, has ventured definitely to side with those modern views which are beginning to gain ground, and which enable us to survey this field of study, formerly of a most confused nature, from one central point of view.

We are now in possession of sufficient facts and arguments to justify us in provisionally adopting the system to be described herein, considering afterwards those cases which do not fit in with this system. No such exceptional case, however, has so far come to our notice, although Apitz sharply defined the modern conception as early as 1939 and 1940.[1,2,3]

We have seen new cases of plasmocytomas within a brief period of time, and one of us, together with Van Dam[6] described a case of paramyloidosis (primary amyloidosis) some years ago that may also be classed with the same group. The clinical data of these cases are given below in the form of tables. It may be gathered from these data that, in these patients, the classical phenomena of multiple myelomas —pains, curvatures, spontaneous fractures, holes in the skiagrams of the bones —were often not predominant.

Many different kinds of multiple myelomas used to be recognized. It was thought that any cell occurring in the bone marrow might give rise to a given kind of myeloma. This conception was mainly based upon an erroneous interpretation of histologic preparation, which did not allow of more refined cellular diagnosis. The difficulty experienced formerly is shown clearly in Reisberman's case:[21] in the sternal puncture he found 586 plasma cells per 1000; but in the histological sections of the spinal marrow no plasma cells could be discovered.

Ever since sternal puncture was introduced into diagnostics, and since, therefore, hematologic differentiation of the various forms of cells has become possible, no further communications concerning all these different forms have appeared, and only one form of myeloma has been described, *i. e.*, the *plasmocytoma.*

As long ago as 1936, Patek and Castle[20] replaced the name myeloma by that of plasmocytoma. They pointed out that, between the different forms of plasma cell tumors, there exists a relation similar to that between the different forms of lymphocytic growths (lymphocytoma, lymphosarcomatosis, lymphatic leukemia).

Rohr[24] says that the typical myeloma is built up from plasma cellular reticulum cells, by which he means that these plasma cells are originated from reticulum cells, which point has no further bearing on our problem. The reticulum cell as understood by hematologists is something different from the conception which the pathologist-anatomist has of it.

Apitz drew up an easily surveyable schematic representation, which is here reproduced (Fig. 1):

1. The locally increased plasma cell exists only hypothetically.

2. It is not certain whether or not the solitary plasmocytoma can occur without diffuse increased plasma cell formation. In any case sternal puncture should be performed *before proceeding to operation.*

3. Diffuse plasmocytosis was, and still is, generally misconceived, and called

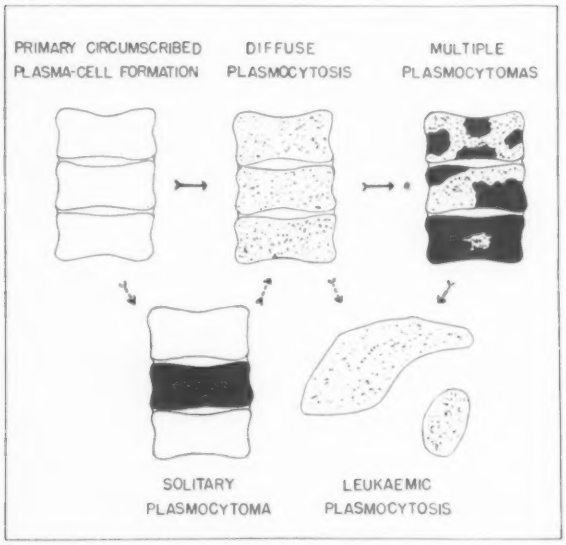

FIG. 1.—Illustrating the interrelation between the different clinical types of plasmocytosis.

either osteoporosis or senile osteoporosis.

With the aid of sternal puncture these diffuse plasmocytoses may be recognized. Pathologic anatomists can safeguard themselves from drawing erroneous conclusions by making slide preparations from patients with osteoporosis, thus enabling the hematologic diagnosis to be made. The results of such an examination in one of our cases are described later on. Naegeli points out that slide preparations should be made as soon as possible after death.

In diffuse plasmocytosis no more than 1 to 3% plasma cells are generally found in the peripheral blood; they may be compared to aleukemic leukemias. They may also turn leukemic quite suddenly, although no more than 50,000 plasma cells per c.mm. are usually found, whereas, in common leukemia, much higher figures are reached. This is a variety of leukemia with "stay-at-home" cells. In these leukemias, too, one frequently finds circumscribed tumors in the bones.[4] It is no longer of great significance whether in these cases we speak of plasma cell leukemia or of plasmocytoma.

4. Multiple plasmocytomas are a long known form of multiple myelomas. They may be clearly seen on Roentgen photos, resembling moth-holes. It is important for the diagnosis that, between the tumors, a diffuse plasma cell formation is said to be found in every case; it is not, therefore, absolutely necessary to strike the tumor itself when performing sternal puncture. When considerable plasma cell formation is found, especially with atypical and polynuclear plasma cells, one may safely diagnose plasmocytoma, remembering that, in such conditions as kala azar, lymphogranuloma inguinale and agranulocytosis increased plasma cell formation also occurs. It is not necessary, therefore—as Mansens would have one do[13,14]—to cut up a corpse millimeter by millimeter so as to exclude the possibility of a single plasmocytoma.

An hour and a half after the decease of our patient I, we made slide preparations from freshly-cut pieces of tissue from the bone marrow, the liver, the spleen, and the lungs. In all these stained preparations we were able to find plasma cells in very large numbers. Mills and Pritchard did the same with a piece of bone obtained by trepanning.[19] In the slides from the bone marrow and the spleen we hardly found any other cells. They have a round nucleus with a distinct nucleolus. The nucleus lies

eccentrically, in a blue, slightly granulated protoplasm, with a lighter-colored area around the nucleus. In fairly large parts we found only naked nuclei. The protoplasm appeared to have run for the greater part, as the intermediary substance showed the same color as the protoplasm of the plasma cells.

This technique of staining cells shortly after death enables the pathologist-anatomist to come to a far more exact diagnosis than the customary pathologic-anatomic section preparations.

II. *Protein metabolism disturbances in cases of plasmocytoma.* Bence-Jones protein is to be distinguished as is well known, from the common variety of albumin in cases of albuminuria in that it precipitates at a temperature of 40° to 60° C., it dissolves completely when boiled, and on cooling below 60° reappears. When, in addition to Bence-Jones protein, there is also albumin of another kind present in the urine, the latter may be precipitated by boiling after adding a few drops of acetic acid. The boiling urine should be filtered immediately. When the clear filtrate cools down to 65° C., it becomes cloudy through the reappearance of Bence-Jones protein, which cloudiness disappears on re-boiling, etc.

Snapper succeeded in demonstrating the presence of Bence-Jones protein very well indeed by adding one-tenth of the volume 20% sulphosalicylic acid before boiling. Schalm,[25] however, points out that, by this method, the reaction turns out positive in a large number of cases of albuminuria; it is probable, therefore, that the Bence-Jones albumin is formed during boiling with sulphosalicylic acid, so that in this way the reaction loses its diagnostic value.

The Bence-Jones protein sooner or later begins to precipitate in the renal tubules; it forms cylinders which may block up the nephrons and tend to set up intrarenal hydronephrosis. When many nephrons have been eliminated in this way the patient dies from uremia.

In from 65 to 80% of sufferers from plasmocytoma Bence-Jones protein is found in the urine. Apitz is of the opinion that it is formed by the plasmocytoma cells. Then it does not occur unless the patient is suffering from a plasmocytoma! The general opinion used to be very different; Bence-Jones albumin has been described in cases of patients with all possible kinds of bone diseases, fractures, shot wounds, in leukemias, nephroses, etc. We are probably justified now in assuming that, in all cases, one of the forms (generally the diffuse form) of plasmocytoma has been either disregarded or misunderstood. None of the descriptions previously given of such cases can stand Apitz's criticism, and no fresh cases have been described in later years.

The work done by Meyler[17,18] is not referred to by Apitz; yet it should not be passed over without comment. Meyler was able to demonstrate the presence of Bence-Jones protein in extracts of normal bone marrow, of pus from empyemas, and in extracts from the cells of a lymphatic leukemia. It is open to question, however, whether the Bence-Jones protein, in these cases, was not created by denaturation from normal protein.

Ellinger (1889), whose method was followed by Meyler, was already of the opinion that, after extraction with alcohol for 14 hours, all proteins except the Bence-Jones protein had been denatured. Meyler himself, for that matter, is fairly critical on this point; he condemns boiling with sulphosalicylic acid, because, in that way, Bence-Jones protein can be made out of all animal proteins.

Even though Bence-Jones protein has been shown to be present in normal marrow the possibility still exists that it is extracted from the plasma cells occurring in the marrow, which appears to be confirmed by the fact that it is present in exceedingly small quantities only. Meyler is of the opinion that Bence-Jones protein can be extracted from lymphocytes; in this case, however, it is incomprehensible that he did not succeed in demonstrating its presence in the spleen. If he succeeds in doing so only in the lymphatic leukemia

cells, then the possibility of any confusion with plasma cell leukemia—which is sometimes hard to identify—must be excluded. As far as we are aware, his followers, at any rate Van Melle and Cornelis,[15] have not succeeded in demonstrating the presence of Bence-Jones albumin in cases of leukemia. The fact that Meyler found Bence-Jones protein in a patient whose knee had been smashed is no evidence either way. A sufferer from plasmocytoma, too, may get a smashed knee, and even more easily than anybody else! At this time Meyler's investigations have largely lost their weight as arguments against the plasma-cell theory.

Paramyloid. Primary amyloid is not similar in distribution to ordinary secondary amyloid, *i. e.*, in patients suffering from chronic suppuration conditions or tuberculosis. It does not occur in the parenchymatous organs (liver, spleen, kidneys), but by preference in the walls of the blood vessels, unless it accumulates arbitrarily in some organ such as the heart, the stomach, the trachea or the lung. Further, paramyloid shows some differences in coloring from secondary amyloid. Apitz takes the view that paramyloid is connected with the presence of one of the forms of plasmocytoma. It is also found deposited in the plasmocytoma tissue. Patients suffering from paramyloidosis often have Bence-Jones protein in their urine. Cylinders of both Bence-Jones protein and paramyloid are cleared away by foreign body giant cells.

With paramyloid the story is like that with Bence-Jones protein. As the occurrence of diffuse plasmocytomas failed to have the attention of investigators, they were ignored; no microscopic examination of the vertebræ was made, and, moreover, microscopic examination of sections was inadequate, so that one contented oneself with the diagnosis "osteoporosis," or "bone marrow rich in cells." In 1940, Van Dam and Kolff described a case of primary amyloidosis with marked osteoporosis of the vertebral column. Apitz's publication suggested to us that we were dealing with a diffuse plasmocytoma, but as unfortunately, the preparations were no longer available, the investigation could not be continued.

Mansens lent good support to the plasmocytoma theory by demonstrating the presence of large numbers of plasma-cells in sufferers from secondary amyloid, either in the diseased organs or in the bone marmor. In Roegholt[23] and Straub's case, however—that of a woman suffering from primary amyloidosis of the tongue—Mansens was unable to find plasmocytoma. In the description of the sternal puncture we read: "double the number of plasma cells and reticulum cells, among which were many large cells with large nuclei, as well as cells with 2 or 3 nuclei." On seeing the preparation one hesitates to make the diagnosis of plasmocytoma; in any event, if this diagnosis is even con sidered, this case is not of any importance in undermining Apitz's hypothesis.

According to Letterer,[10,11] amyloid precipitates in the body when there exists a disproportion between a large quantity of a certain antigen, broken-down body protein ("eingeschmolzenes Korpereigenes Eiweiss"), and too small a quantity of antibodies. Only Letterer's view, that this antigen is probably created by leukocytes, should be revised; it must be the pathologic protein products of the plasma cells which serve as antigen.

Hyperproteinemia. A very high globulin content of the blood is found in many patients with plasmocytomas. It is probable that in such cases we are not dealing with any raised globulin content, but an accumulation of pathologic globulin (paraprotein) in the blood (Bondsdorff).

Intracellular accumulation of protein. In the plasmocytoma cells and in the cells of the convoluted tubules the presence of accumulations of protein or crystals may sometimes be demonstrated. As regards colorability, these protein precipitates evince a strong resemblance to Bence-Jones protein and to paramyloid. They strongly indicate the probability that this protein is formed in the plasmocytoma

cells. Very good pictures are given by Apitz and Brass.[4] The latter's supposition, that these albuminoid formations are actually body proteins resorbed into the plasmocytoma cells, is both incomprehensible and insufficiently founded.

Apitz points to the many properties which the above-mentioned proteins have in common, and proposes to call them "paraproteins."

The paraproteins constitute a group of closely kindred pathologic protein occurring in plasmocytoma; they readily precipitate, are crystallized fairly readily, and may all be colored with congo-red. The *paraproteinoses*, therefore, are a group of diseases of the protein metabolism occurring exclusively in cases of plasmocytoma; Apitz speaks of "*paraproteinuria*" (Bence-Jones proteinuria); "*paramyloidosis;*" "*paraproteinemia,*" and *intracellular accumulations of "paraprotein.*" One might wonder if any conclusions could be drawn, with respect to the origin of normal serum protein from the pathologic protein formation described above. In normal plasma cells, too, enclosures and crystals of protein are to be found. In cases of trachoma, indeed, paramyloid might be formed locally by inflammatory plasma cells; we already have pointed to Mansen's investigations. Normal serum protein may perhaps be formed by normal plasma cells. The pathologic plasma cells of the plasmocytoma are the formers of paraprotein. Those cells which morphologically differ

TABLE 1 CLINICAL AND PATHOLOGIC DATA OF 4 CASES OF PLASMOCYTOMA

	Name, Sex and Age			
	Van den B. M., 50 yrs.	Post M., 67 yrs.	V. O. M., 53 yrs.	V. D. V. M., 58 yrs.
Anamnesis and course of disease	12 recurring pneumonias and slight bleeding from nose and gums; no bone symptoms	Abdominal pain with constipation; 6 wks. backache	Anemia; backache	For 1½ yrs. severe backache, gradually increasing in severity; emaciated; vomiting since 5 wks. ago
Objective findings	Pneumonia; no further abnormality	Slight kyphosis; pressure on vertebral column painful	Anemia only	Vertebra and other bones extremely painful on pressure; amyloidosis of smaller arteries, especially in head
Hemoglobin, etc.	Hb., 33%; CI, 1; lcts., 3000 to 6000; plasma cells, 1%; lymphocytes, 51%; thrombocytes, 24,000	Hb., 70%; lcts., 7300; plasma cells, 0%; lymphocytes, 18%	Hb., 23%; lcts., 5200; thrombocytes, 63,800	Hb., 60%; CI, 1; lcts., 9200; plasma cells, 0 %; lymphocytes, 22%
Bone marrow function	Many pathologic plasma cells	Many pathologic plasma cells	Many pathologic plasma cells	?Marrow rich in cells on autopsy
Erythrocyte sedimentation rate and globulin content	Sed. rate, 150 to 165; globulin, 12%	Sed. rate, 98 to 133; globulin, 8.5%	Sed. rate, 63 to 135; globulin, 4.36%	Sed. rate, 73; globulin 2.1%
Bence-Jones albumin in urine	++	Alternately + and −	Negative	Probably positive
Other urine abnormalities	Alb., 3.5%; erythrocytes	Sporadic erythrocytes and leukocytes	Albumin	Albumin, 5%
Roentgen, osseous system	Diffuse osteoporosis of vertebral column and round holes in tubular bones and pelvis	Only diffuse osteoporosis of entire vertebral column	Osteoporosis of vertebral column and pelvis	Osteoporosis of vertebral column and pelvis with fish vertebræ and infractions
Cause of death	Uremia	Pneumonia	Died at home 6 mos. after admission	Cachexia
Miscellaneous	Auto-agglutination of erythrocytes in Hayem's fluid; at autopsy: plasma cells in internal organs	.....	Spinal fluid: total albumin 64 mg. % (norm. 18 to 24); out of this globulin, 45 cells ¼; Pandy slightly +	Paramyloidosis of artery walls and stomach wall

only little from normal plasma cells (*e. g.*, the cells of plasma cell leukemia) would not tend to give rise so frequently to the occurrence of paraproteinoses (Bence-Jones proteins, etc.). It will be interesting in the future to see whether a given morphologic type of plasma cell induces a given type of paraproteinosis.

Summary. A new concept of plasmacytosis has evolved during recent years, integrating the various clinical forms of this disease. Whether there is focal, diffuse, or leukemic plasmocytosis, sternal puncture will reveal a general increase in plasma cells and is usually diagnostic. Illustrative cases are reported. The production of Bence-Jones proteinuria, hyperglobulinemia, and primary amyloidosis are discussed in the light of present knowledge.

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ADENINE: ITS FAILURE TO STIMULATE HEMOPOIESIS OR TO PRODUCE PELLAGRA IN A CASE OF PERNICIOUS ANEMIA*

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For many years we have been studying various synthetic substances and natural products to determine whether or not they induce blood regeneration in various types of anemia. During the course of our observations we have noted that a number of chemical substances stimulated hemopoiesis in persons with Addisonian pernicious anemia, nutritional macrocytic anemia and the macrocytic anemia of sprue. One of these, thymine (5-methyl uracil), is a pyrimidine base and is a constituent of thymonucleic acid.[4] After finding thymine effective, we turned our attention to adenine, which also occurs in thymonucleic acid as the base of a nucleotide. It is a purine base, 6-amino purine, as seen in the chemical formula shown in Figure 1.

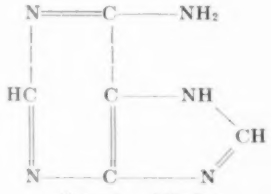

Fig. 1.—Adenine.

Adenine is widely distributed in plant and animal tissues. As a component of thymonucleic acid, it enters into the structure of the nuclei of all animal cells.[2] It is otherwise present in the body in the free state and as nucleotides which, to some extent, are constituents of enzymes and co-enzymes. Two of them, co-enzymes I and II, are pyridine nucleotides which apparently are formed by living cells from a combination of nicotinamide, ribose, adenylic acid and phosphoric acid.[5] The concentration of these co-enzymes in the blood and striated muscles decreases in the pellagrin, and treatment with nicotinamide restores it to normal levels.[1] Spies and his associates also have shown that the administration of co-enzyme I relieves pellagra.[3]

Recently Raska reported that black-tongue in dogs developed within 7 to 21 days following the administration of from 200 to 500 mg. of adenine daily.[3] He believes that this occurred as a result of adenine combining with constituents of the vitamins or their precursors, thus preventing their utilization in the animal. He refers specifically to the possibility of an interference with the formation and activation of alloxin adenine dinucleotides, of the phosphopyridine dinucleotides (co-enzymes I and II) and of the nucleoproteins.

In view of these findings it seemed worthwhile to report our observations on the effect of the oral administration of adenine to human beings. After administering from 5 to 50 mg. each day for from 4 to 10 days to each of several persons with macrocytic anemia in relapse and observing neither toxic manifestations nor blood regeneration, we administered it in larger doses to a patient with Addisonian pernicious anemia in relapse whose case history follows:

Case 1. The patient, J. D., a 67 year old, married, colored bricklayer, was admitted to the hospital on July 26, 1946 because of symptoms related to pernicious anemia in

relapse. He had been hospitalized on 3 previous occasions, once for an inguinal herniorrhaphy in 1945, and twice (September, 1944 and September, 1945) for the treatment of anemia. At the time of his first admission, he complained of progressive weakness, dyspnea on exertion, slight soreness of the tongue, vague abdominal distress and loss of weight which had begun 9 months previously. He had achlorhydria and achylia after histamine stimulation, and a macrocytic anemia with maturation arrest of the bone marrow cells at the megaloblast early-erythroblast level which responded well to refined liver extract.

When he stopped maintenance therapy, his anemia relapsed and he was readmitted to the hospital for treatment in September, 1945. At that time synthetic folic acid in doses of 50 mg. twice a day was effective in producing blood regeneration and normal blood values. Freedom from symptoms continued until he again stopped maintenance therapy in April, 1946. From that time until his admission to the hospital in July, 1946, there was a recurrence of the following symptoms: general weakness, dyspnea on exertion, slight soreness of the tongue, anorexia and paresthesia of the lower extremities. On admission he appeared rather weak but he was alert mentally and was in no apparent distress while at rest. The conjunctivæ and buccal mucosa were pale; the sclera was cloudy but not icteric; the optic fundi were normal; there was slight redness at the tip of the tongue and the papillæ generally appeared hypotrophic; a systolic murmur was audible over the apex of the heart and blood pressure was 150/80 mm. Hg.; radial arteries were moderately firm; and the lungs were clear and the abdomen negative. The knee and ankle jerks were hypoactive and vibratory sensation was impaired at the knees and ankles.

The initial blood counts were: RBC 1.86 million, WBC 4350, Hg. 7.0 gm. (45%), Reticulocytes 0.6%, PCV 22%, MCV 118. Blood NPN 23; Kahn negative; icteric index 10; glucose tolerance test normal curve; stool negative; gastro-intestinal series negative; gastric analysis—achlorhydria after histamine stimulation. Urinalysis showed specific gravity 1.020, acid reaction, albumin and sugar negative and microscopic examination negative.

Three days after admission to the hospital on July 29, 1946, 2½ gm. of adenine hydrochloride* twice a day orally was started. Three days later he complained of anorexia and slight nausea, and 5 days later of slight dizziness and a bad taste in his mouth. Meanwhile there were no significant changes noted physically, and he spent considerable time up and about the ward. During the night of the 6th day of adenine therapy, the patient in the next bed reported that this patient (J. D.) had a very restless night, "talked out of his head," vomited, passed a stool in the bath tub and complained that he had trouble thinking and talking. The following morning he appeared very apprehensive and restless and was unable to talk clearly but he seemed fully conscious and attempted to coöperate. The physical findings were as follows:

His eyes at times deviated involuntarily but the pupillary reaction and fundi were normal. The tongue was pink at the tip and edges but did not deviate when protruded and was not tremulous. The lungs were clear. The heart rate was 112, the rhythm normal and the blood pressure 170/110. Neurological examination showed mild rhythmic muscle group contractions involving chiefly those of the forearms and those of mastication; muscle tone generally seemed somewhat increased; however, when an extremity was placed at full rest, considerable relaxation could be obtained; the knee jerks and ankle jerks were slightly more active than on admission but were still normal. No abnormal reflexes were obtained. (The adenine was discontinued—the total dose given was 32.5 gm.) A urine specimen at this time showed: pH 7.5; specific gravity 1.010; albumin trace; sugar negative; no RBC or WBC; sediment thick with amorphous material. The blood NPN had risen from 23 mg. per 100 cc. before adenine was started to 135 mg. per 100 cc.

During the next 24 hours he became worse. Although conscious, he was unable to speak; moderately severe clonic convulsive seizures involving chiefly the upper extremities, cervical, shoulder girdle and abdominal muscles required sodium luminal therapy; the reflexes remained physiologic; and the blood pressure continued elevated. There were no physical signs of increased intracranial pressure and no meningeal signs. There were at no time

* Adenine hydrochloride was furnished by Dr. Earl D. Stewart of Schwarz Laboratories, Inc.

any signs of hemorrhage or ulceration of the eyes, buccal mucosa, skin, gastro-intestinal or genito-urinary tracts; there were no signs of dermatitis and no clinical evidence of acidosis. The mild degree of glossitis present on admission was not altered. Urine specimens contained from a few to many white blood cells, hyaline casts, and much amorphous material and some crystals thought to be uric acid. The blood NPN reached a peak of 175 mg. per 100 cc.; blood uric acid 9.8 mg. per 100 cc.; the blood CO_2 combining power 63 vol. per 100 cc. The spinal fluid was normal and the blood Wassermann negative. His temperature rose from 99° F. during the first 24 hours of symptoms to 101° F. where it remained for a period of 48 hours. About 72 hours after the onset of the previously mentioned symptoms, he began to improve, first with subsidence of the convulsive phenomena and then of the dysarthria or motor aphasia. Within another 24 hour period, his blood pressure had dropped to 125/75 mm. Hg., he talked without any difficulty and muscle tone was entirely normal. He did not appear as alert mentally as he did prior to adenine therapy but he was coherent and oriented. He did not rememder what had taken place during the preceding days.

Five days after toxic symptoms appeared, the blood NPN had dropped to 152 mg. per 100 cc. and 4 days later to 90 mg. per 100 cc. It continued to fall to 38 mg. per 100 cc. 30 days after symptoms began. During the first 15 days, the urine specimens contained from a few to many white blood cells, hyaline casts, large quantities of amorphous material and some uric acid crystals. Within 10 days tests for albumin were negative. The highest specific gravity recorded was 1.011.

After adenine was discontinued, therapy consisted of 2 transfusions, intravenous saline and glucose solutions, sodium luminal to control the convulsive phenomena, and folic acid 10 mg. intramuscularly. Eight days after folic acid was started, the reticulocyte count was 5% but a peak count of 15.2% was not obtained until the 14th day of therapy. The white blood cell count remained below 5000 until the 11th day of folic acid therapy when it was 10,900; it remained around this level for 3 days. The red blood cell count and hemoglobin increased very slowly to 2.71 million and 10.1 gm., respectively, 7 weeks after folic acid therapy was started.

During the 10 month period following his discharge from the hospital, he had no recurrence of symptoms and signs. The highest blood pressure recorded was 150/80 mm. Hg.; the blood NPN ranged from 32 to 38 mg. per 100 cc.; the urinalyses were negative for albumin, WBC and RBC, but the highest specific gravity was 1.017. No abnormal eye ground changes or signs of cardiovascular disease, other than firmness and beading of radial arteries, were noted. No evidence of residual central nervous system disturbance could be detected. Fourteen weeks after folic acid therapy was begun, his blood counts were: RBC 4.29 million, Hg. 14.1 gm. (92%) and WBC 6400.

Summary of the Case. A 67 year old colored man who has pernicious anemia that responded at one time to liver extract and at another time to folic acid was given 2½ gm. of adenine hydrochloride the first day of therapy and was given 2½ gm. twice a day each of the succeeding 6 days (a total of 32.5 gm.). Evidence of toxicity which began on about the 5th day of therapy consisted of a bad taste in his mouth, anorexia, mental confusion, emesis one time, aphasia, clonic convulsive seizures, transient oliguria, elevation of blood pressure, elevated blood NPN and uric acid and abnormal urinary findings. Progressive improvement began within 72 to 96 hours after adenine was discontinued and he was given therapy consisting of 2 transfusions, intravenous saline and glucose solutions, sodium luminal and folic acid.

Comment and Conclusions. Following the ingestion of large doses of adenine, a patient with Addisonian pernicious anemia in relapse developed uremia. Neither blood regeneration nor any evidence of pellagra developed. These findings are of interest in that they show clearly that acute toxic symptoms arise following large doses of adenine hydrochloride and that no hemopoietic effect was observed. Under the conditions of this study and with recognition of the limitations of a single

case study, it may be stated that the findings do not support Raska's contention that adenine produces blacktongue in dogs but they do support his observation that animals develop nitrogen retention following adenine administration.

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PROTHROMBIN ACTIVITY OF "STORED HUMAN BLOOD"

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The use of human blood stored in blood banks has almost completely replaced the use of fresh citrated blood or direct whole blood transfusions in the average general hospital today. From *in vitro* studies of "stored blood," many investigators have reported results which show it to be deficient in prothrombin.[13,14,15] The purpose of this investigation is to determine the degree of prothrombin deficiency found in "stored" human blood. We have undertaken a study on 50 different samples of stored human blood. It is found to be adequate in prothrombin activity upwards of 5 to 7 days.

The toxic manifestations apt to follow the clinical use of the anticoagulants heparin and dicoumarol, require special forms of treatment. The minor bleeding tendencies such as hematuria, ecchymosis and epistaxis can readily be controlled by discontinuing the drugs. If this fails, or when the bleeding is due to heparin overdosage, protamine may be given intravenously.[6] When dicoumarol is the toxic factor, vitamin K in massive doses (60 to 72 mg.) may be given intravenously. However, gross hemorrhage, and in particular that associated with shock and hepatorenal failure, will not respond to these measures. Dicoumarol hypoprothrombinemia under these conditions is progressive and severe. This situation demands the replacement of whole blood which should contain the normal amount of prothrombin. A similar problem exists in cases of hypoprothrombinemia of hepatocellular origin unresponsive to vitamin K.

In reviewing the literature on the activity of prothrombin in "stored" or "banked blood," we have found varying opinions as to the content of prothrombin remaining; that is to say, the rate of prothrombin conversion at various periods of storage. In some of the "stored blood" studies reported, oxalated blood was used.[1,13] But, the decalcifying agent used in "stored blood" is sodium citrate. Other reports concern the study of a single specimen. It is apparent that a larger series of "stored blood"should be investigated under actually encountered blood bank conditions, and with the same anticoagulant and preservative which are used today by blood banks in general.

The two common methods used to study prothrombin are: (1) The Warner, Brinkhaus, and Smith, or 2-stage method which extracts the fibrinogen present in the plasma and then converts the prothrombin to thrombin.[17] The final stage occurs with the addition of a constant amount of fibrinogen to the thrombin previously formed, resulting in a fibrin clot. (2) Quick's method and the Link-Shapiro modification of Quick's, which determine the rate of prothrombin conversion.[11,2] The Warner, Brinkhaus, and Smith method ascertains quantitatively the amount of prothrombin present and may be questioned in a study of this nature. The other constituents such as platelets, thromboplastin, activators and inhibitors are not measured by the 2-stage method. These substances are present in "stored blood" and may alter the prothrombin

activity. The results of the Quick method and the Link-Shapiro modification of it, are affected by the aforementioned constituents.

Investigators using the Warner, Brinkhaus, and Smith method on several bloods, found a diminution in the amount of prothrombin present as follows: blood stored 9 to 12 days—75 to 91% of normal;[10,18] 18 to 25 days—50 to 61% of normal;[10,18] and by the 37th day, 40% of normal.[19] Those using Quick's method on a somewhat greater number of blood samples found a wide variation in the speed of prothrombin conversion. Oxalated blood stored 24 hours, 50% of normal.[13] Citrated blood stored 1 to 3 days—35 to 73% of normal.[10,14] On the 7th day, 25 to 55% of normal;[14,15] 9 to 13 days—20 to 50% of normal;[14,15] 8 to 24 days—14% of normal;[10] 28 to 38 days—50% of normal.[3] The wide variation resulting from Quick's method makes it difficult to arrive at a definite conclusion as to the activity of prothrombin in "stored blood."

We have undertaken the investigation of 50 units of "stored blood" selected at random. Each unit was examined daily during a period of 21 days. At this hospital blood is considered suitable for transfusion for 21 days.

Method. From each of 50 healthy donors 500 cc. of blood was obtained. Each unit was thoroughly mixed with 125 cc. of acid-citrate-dextrose solution following the usual blood bank technique. Acid-citrate-dextrose solution has been reported as being the best preservative for whole blood.[5] Seventy per cent of the cells so preserved survive after 35 days and 65% after 39 days of storage.[5] Under aseptic precautions 18 samples, 4 cc. each, were transferred immediately to rubber-capped, sterile vacuum tubes. The specimens were stored at 4° C. ± in the blood bank refrigerator. An equal vacuum was used for the tubes and the donor storage bottles.

The technique of Link-Shapiro modification of Quick's method, using rabbit lung as the source of thromboplastin was used.[2] The thromboplastin used gave an average whole plasma prothrombin time of 12.4 seconds. An original lot of thromboplastin and chemicals was used throughout this study. The same technician performed all determinations. The whole plasma prothrombin time and 12.5% plasma prothrombin time (made

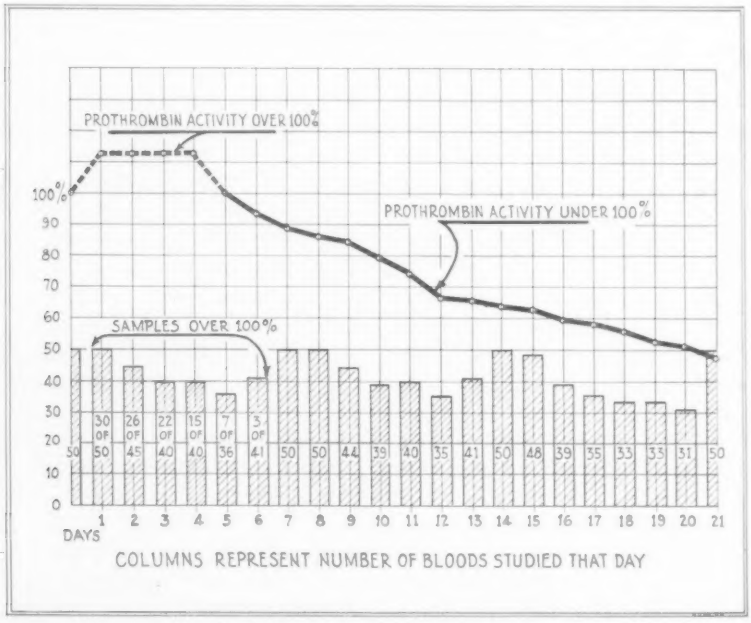

FIG. 1.—Whole plasma prothrombin activity.

by diluting whole plasma with physiologic saline) were performed on each individual blood sample daily with the exception of a few. This may be noted in Figures 1 and 2. The error allowed for whole plasma is 0.5 second and for the 12.5% plasma, 1 second. It is believed by some that 12.5% plasma is more sensitive than whole plasma to minute changes in prothrombin and is therefore a more sensitive indicator of the rate of prothrombin conversion.[16]

On the day each blood was taken an individual dilution curve (graph) was made with physiologic saline and plasma according to the method outlined by Quick.[12] From these graphs the percentage prothrombin activity was read for each individual subsequent determination of whole plasma prothrombin time.

Results. The percentage prothrombin activity of whole plasma may be seen in Figure 1 for each day. It can be noted that the prothrombin activity is over 100% for the first 4 days following storage and 100% for the 5th day. However, a few continued to show over 100% activity through the 6th day. After the 5th day there is a gradual drop of prothrombin activity to 84.8% on the 9th day, followed by a more rapid drop to 66.2% on the 12th day, after which the drop is gradual again to 47.7% by the 21st day. Any possible increase in activity over 100% cannot be expressed numerically during the first 4 days, as the curve of prothrombin activity is maximum at 100%. For these 4 days the whole plasma prothrombin time is shorter (more active) than on the day the blood was drawn.

The 12.5% plasma, as demonstrated in Figure 2, shows a somewhat similar change in the rate of prothrombin conversion, although not quite as dramatic. For the first 5 days following storage of whole blood there is a decrease in the dilute prothrombin time (increased prothrombin activity) beyond the limit of technical error. On the 6th and 7th days there is no change in dilute prothrombin time as compared to the day the bloods were taken. From the 8th to the 21st day there is a slow rise in the dilute prothrombin time.

Discussion. Crosbie *et al.* found an increased coagulability of "stored blood" during this same period;[3] Banfi *et al.* and

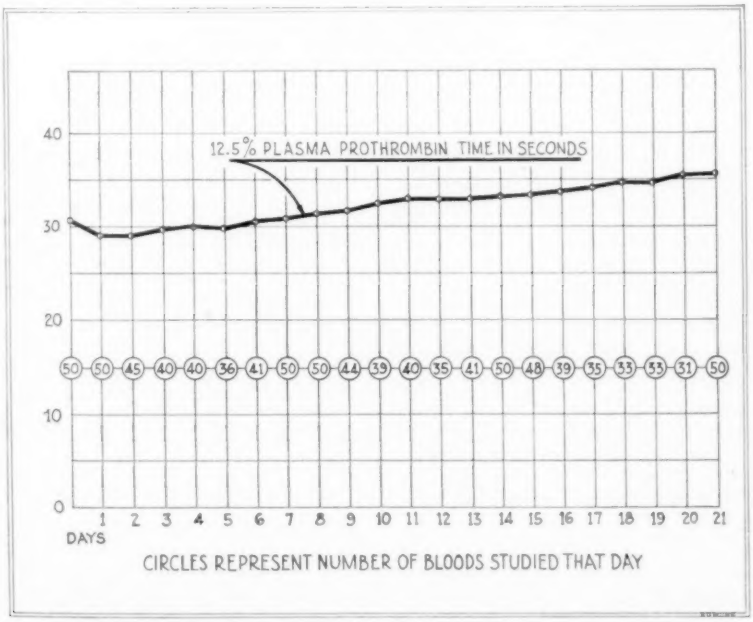

FIG. 2.—12.5% plasma prothrombin time.

Kolmer found increased prothrombin activity within 24 hours of storage.[1,8]

Thromboplastin is essential for the mechanism of prothrombin conversion as well as ionizable calcium. Crosbie *et al.*, Drew *et al.*, and Kolmer have shown that platelets begin to disintegrate in "stored blood" within 24 hours and continue to disintegrate for 5 or 6 days.[3,4,8] As platelets disintegrate thromboplastin is liberated. The excess thromboplastin is probably responsible for the more rapid prothrombin conversion as illustrated in both the whole and dilute plasmas during the first 4 to 5 days, respectively.

Lord, Andrus, and Moore demonstrated in dogs and *in vitro* that, "the changes in the total content of prothrombin in the plasma of a recipient after a transfusion are dependent on the prothrombin content of the plasma of the donor, and may be calculated on the basis of addition."[9] The amount of prothrombin contained in 500 cc. of blood is relatively small when compared with the total quantity of prothrombin in the normal human. Theoretically, a single transfusion should have little effect upon the prothrombin present in the recipient. However, Karabin *et al.* have observed several instances where a marked improvement occurred in cases of hypoprothrombinemia following the use of "stored blood."[7]

The results reported in this investigation are from *in vitro* determinations of the activity of prothrombin in "stored blood." It cannot necessarily be concluded from this experiment that the use of "stored blood" during the period of hyperprothrombin activity introduces hypercoagulable factors in the recipient.

Conclusions. (1) Prothrombin activity or rate of prothrombin conversion in "stored" or "banked blood" is increased during the first 4 to 5 days and is normal from the 5th to the 7th day. The increased prothrombin activity during the first few days of storage is probably due to the disintegration of platelets which liberate thromboplastin. Thereafter, the prothrombin activity slowly falls to 47.7 % by the 21st day.

(2) It is practical to use "banked blood" for hypoprothrombinemia, or bleeding associated with it, as an agent containing normal hemostatic qualities, during the first week of storage.

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THE SIGNIFICANCE OF THE PAUCITY OF SICKLE CELLS IN NEWBORN NEGRO INFANTS

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Since the sickle cell trait is inherited as a Mendelian dominant in negroes[24] and is therefore presumably present from the onset of hematopoiesis in fetal life, sickle cell disease should occur in infancy as often as later in life. Although McGavack and Nussbaum[31] found that 50% of 214 reported cases had symptoms of their disease before the age of 2 years, there are very few cases reported before the age of 6 months. Graham and McCarty[20] report the autopsy of a 4 month old negro infant who died of bronchopneumonia, whose spleen was said to show typical findings of sickle cell disease. Wollstein and Kreidel[46] mention death due to bronchopneumonia in a 3 month old baby with sickle cell disease. Unfortunately clinical data are lacking in both these cases. Tomlinson[40] reports that sickle cell anemia was found at autopsy in 2 cases in the age group of 1 to 6 months in his investigation made at the Canal Zone. We have found two other reports[10,25] in the literature of hospital admissions for sickle cell disease before the age of 6 months, and six others[2,7,11,12,13,30] in the succeeding age period of 6 months to 1 year. The paucity of cases in infancy is surprising in view of the frequency of hospital admissions in later childhood. Several of our patients have had more than 20 periods of hospitalization for the management of their crises. However, there have been several cases in older children[5,21,22,38,46] where there was a history of symptoms beginning at the age of 6 to 12 months. Often the story is given of being "sickly as long as I can remember," but the exact data for infancy is not known.

In a study of the baby of one of our sickle cell anemia patients, we found only 6% sickling at birth, with a gradual increase to 90% at 4½ months. When last seen at 6 months he was still well and had no hematologic evidence of sickle cell anemia. In 26 reported deliveries of patients with sickle cell disease, sickling was noted to be present in 8 of the infants,[23,27,28,36,37,39] but the percentage of sickled red cells was mentioned only once,[29] in which case it was given as 1%. Sharp and Schleicher[34] report a baby in whom no sickling was found at birth, but in whom sickling was found to be present at the age of 4 months. The largest study of sickling in newborn negroes was done by Diggs and co-workers,[16] who found sickling in 6 out of 159, a percentage of 3.8. This is considerably lower than their over-all figures of 8.3% for 2539 negroes of all ages. Although the percentage of sickled red cells in each preparation was not noted, the comment was made that sickling in newborns was "less marked and developed more slowly than in adults with the trait." Graham and McCarty[19] found sicklemia in 5 out of 6 newborn infants of mothers with sicklemia. Beck and Hertz[4] found sicklemia in 1 out of 5 newborns tested, and stated that there was only 5% sickling in the sealed preparation. Since the red cells of adults with the trait are known to sickle 100%, the scattered evidence presented seems to indicate that

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sickling is incompletely developed at birth.

Given a newborn who shows the sickling trait, there is at present no certain method for predicting whether he will later develop the disease; for it is not known whether the means of differentiation (all of which depend upon differences in sickling threshold to oxygen tension[35,44]) are valid at that period. Geneological studies have not been very helpful, since the attractive theory that homozygosity might be responsible for the disease, in contrast to heterozygosity for the trait, is not well supported factually.[32] In view of the generally accepted estimate that, of the 7.3% of negroes who have sicklemia, only 1 out of 40[16] will have the disease, it is not statistically profitable to make a study of negro newborns in the hope of finding one who will develop sickle cell disease. Indeed, there are no records of cases of sickle cell anemia which have had careful hematologic studies since birth. However, it seemed possible that the study of sicklemia in the newborn negro infant might indirectly throw some light on the problem of the development of sickle cell disease.

Methods. Sickle cell preparations were made on 226 consecutive negro newborn infants in the nursery of Kings County Hospital. The mothers on the maternity service were used as the control series.* Finger blood from the mothers and heel blood from the infants was used. The standard sealed preparation[18] was made, using clean glass slides and No. 1 cover slips. For the first few cases a vaseline seal was used, but subsequently paraffin was substituted because it eliminated the tendency for the blood to retract at the edges of the cover slip. All preparations were made in duplicate, incubated at 37.5° C., and read for sickling at 24 hours. Only the typical sickled cells with long bizarre processes were counted, doubtful cells of odd shapes being excluded. The percentage of sickled cells was determined from counting 200 red blood cells in the areas which showed maximum sickling. Pressing too hard on the cover slip was found to favor disintegration of the sickle cells; in infant blood with macrocytic red cells and tendency to the formation of thicker drops, it was particularly important to avoid this pressure when making the sealed slide. Sickling preparations are notoriously capricious[17,20,35] so that consistent procedure in the smallest detail is of the utmost importance. It is realized that determining the percentage of sickled cells does not yield exactly the same figure in each preparation made from a given sample, but differences of the order of 10 to 20% can be interpreted as being significant. It was found that the blood of the newborns sometimes required 48 hours to reach maximum sickling, so that the percentage of sickling was noted at 24, 48, and 72 hours. At 72 hours the sickling usually had not increased, but had begun to diminish, and often partial hemolysis had set in; these figures are therefore not included in this paper. In the case of the mothers, maximum sickling occurred within the first 24 hours.

The hemoglobin values of the mothers were obtained from their charts. The Haden-Hausser method was used.

Results. Of the 226 negro mothers examined, 18 (8%), showed sicklemia; the data on them is presented in Table 1. None had clinical or hematologic evidence of sickle cell disease. The percentage of sickled red cells was usually 100%, and at 24 hours exceeded 84% in every case.

TABLE 1.—MOTHERS WITH SICKLEMIA (18 OUT OF 226 CASES)

Case No.	Age, years	Hgb, gm. %	Sickling % at 24 hrs.
1	19	10.5	96
5	24	10.0	100
8	19	10.0	84
18	27	9.0	100
52	31	..	100
67	28	9.5	100
116	19	10.5	100
121	24	8.5	100
123	17	11.0	100
128	22	9.0	100
130	18	10.5	100
140	15	9.5	63*
143	21	10.0	86*
155	27	10.0	93
167	22	10.5	94
179	22	11.0	100
180	32	10.5	96
220	19	10.0	100

* Read at 72 hours.

* We are indebted to Dr. C. A. Gordon of the Long Island College Division of the Obstetrical Service and to Dr. L. Krahulik and Dr. E. J. Basile of the Long Island College Divison of the Pediatric Service of Kings County Hospital for their kind permission to study these patients.

Of the 226 infants examined, 19 (8.4%), showed sicklemia (Table 2). The case numbers in the table are the same as those of the corresponding mothers except for the addition of the letter "a." Maximum sickling varied from 0.5 to 29.5%, with a mean of 11%. The tendency for the last figures to be higher may be accidental or may be due to improved technique. In 6 instances blood was also sickled by the gas chamber method of Hahn and Gillespie,[21] and the percentage of sickled erythrocytes was found to be essentially the same as that of the sealed preparation. The infants with sicklemia were all healthy full term babies.

TABLE 2.—NEWBORNS WITH SICKLEMIA (19 OUT OF 226 CASES)

Case No.	Age, days	Sickling		Sicklemia in mothers
		% at 24 hrs.	% at 48 hrs.	
4a	3	2 0	..	No
5a	2	4 0	..	Yes
24a	2	0 5	..	No
35a	3	1 0	1 0	No
37a	3	1 0	8 5	No
40a	1	1 0	7 0	No
67a	1	5 0	..	Yes
85a	2	8 5	11 0	No
116a	1	2 5	4 5	Yes
128a	1	1 5	1 5	Yes
129a	1	2 5	19 0	No
153a	2	19 0	19 0	No
154a	3	14 5	20 5	No
155a	2	12 5	15 0	Yes
167a	1	19 5	19 5	Yes
179a	1	3 5	..	Yes
180a	2	12 5	21 0	Yes
181a	1	29 5	29 5	No
220a	1	16 5	29 0	Yes

Discussion. The incidence of sicklemia in the newborn negroes in our series agrees very well with that of the mothers, being 19 and 18 respectively out of 226 (8.4 and 8%). These figures compare closely with the usual figure quoted for this country—7.3% of a series of 8423 negroes.[16] Of the 19 babies with sicklemia, 9 had mothers with the trait—a figure which would be expected for a Mendelian dominant characteristic.[24]

Despite the fact that the incidence of sicklemia of the infants and adults was almost identical in both groups two important differences with respect to the sickling were noted. First, the sickling of the infants' red cells often required 48 hours to reach a maximum instead of the 24 hour period required for the mothers' red cells. This presumably means that a lower oxygen tension[21] is required for the sickling of the infants' cells. It has been shown that there is a significant shift to the left of the oxygen dissociation curve of oxyhemoglobin at birth, which gradually reaches adult values at the age of 6 weeks.[14] The presence of fetal hemoglobin might then explain the longer period necessary for the sickling of newborn red cells.

The second difference noted was that, of the mothers who had sicklemia, the red cells showed 84 to 100% sickling, in contrast to those of the infants which showed only 0.5 to 29.5% sickling. The greater affinity of fetal hemoglobin for oxygen should not account for the low percentage of sickled red cells in newborns with sicklemia, since the maximum percentage of sickling could not be raised over that of the sealed preparation by use of the gas chamber method where oxygen can be excluded entirely from the system.

It might be thought that immaturity of many cells in the newborn would reduce the sickling tendency, as there are in the literature reports that normoblasts and even reticulocytes fail to sickle. Careful study[43] has shown that, while the velocity of sickling may be retarded in immature cells, the percentage is the same as in older ones. The blood of these infants contained no high percentage of immature cells and another explanation must be sought.

It is well established that human fetal hemoglobin differs chemically from adult hemoglobin. Differences have been demonstrated with respect to alkali denaturation,[6] histidine content,[42] immunological properties,[15] the oxygen dissociation curve,[14] crystallization,[33] and sedimentation constants and electrophoretic mobilities.[1] It is thought that these differences are due to variation in the chemical structure of globin, especially since spectroscopic analyses have failed to show

differences in the prosthetic group of hemoglobin.[26] Brinkman *et al.*[8] have shown that newborn blood contains about 80% of the fetal alkali resistant hemoglobin. This was still present in two infants 3 months old, but was absent in one of 7 months.[9] Trought[41] in a similar investigation found that it disappeared as early as 4½ months. The theory that at once presents itself is that fetal hemoglobin is unable to produce sickling, and that the sickling trait progressively becomes 100% with the gradual formation of the new red cells containing the adult type of hemoglobin which possesses the sickling property. This hypothesis is further strengthened by the fact that the estimated life span of the erythrocyte is 4 months.[45] This fits in well both with Trought's observation that the fetal hemoglobin disappears at 4½ months and with our finding of an infant who developed 90% sickling at 4½ months in comparison with the 6% sickling at birth. Whether this last instance represents the usual course of events can be decided only by following the percentage of sickle cells from birth through one year in a series of infants, a study now under way.* Whether the sickling in infancy follows a different pattern in those infants who will develop anemia and in those merely showing the trait will take some years to determine.

Since an oxygen tension of 45 mm. Hg. is taken to be the threshold for sickling in patients with sickle cell disease,[35] the much lower oxygen tension that occurs *in utero*[3] should cause complete sickling and thus be incompatible with life. In fact, if the same low tension of 16 mm. is achieved in the human fetus as in the sheep, sickling *in utero* should occur even in those with the sickling trait only, since the oxygen tension threshold in these cases is estimated to be 18 mm.[35] However, we could find no cases in the literature of pathologic findings of sickle cell anemia in autopsies of newborns and stillbirths. The youngest autopsied cases were infants 1 month,[10] 3 months,[25] and 4 months[20] old, the first being complicated by acute otitis media, and the last two by bronchopneumonia. It seems likely then that fetal hemoglobin lacks the sickling properties of adult hemoglobin, thereby preventing automatic extinction of sickle cell disease from deaths *in utero*, and partially protecting the infant in the first 4 months of life during which time it gradually disappears from the blood.

Summary. 1. A study was made of sickling in 452 consecutive negro newborns and their mothers: 8% of the mothers and 8.4% of the infants showed sicklemia.

2. The red cells of mothers with sicklemia showed 84 to 100% sickling, while those of the newborns showed only 0.5 to 29.5%. The red cells of the latter also required a longer time to attain maximum sickling.

3. It is suggested that these differences are due to a chemical difference between fetal and adult hemoglobin because:

(*a*) Fetal hemoglobin as tested by the alkali denaturation method differs from adult hemoglobin and does not disappear from the blood until 4½ months. The oxygen dissociation curve of fetal hemoglobin is shifted to the left.

(*b*) The life span of the erythrocyte is about 4 months. If adult hemoglobin begins to be manufactured at birth, 4 months would elapse before it would entirely replace fetal hemoglobin.

(*c*) In one case of sicklemia followed from birth, sickling increased progressively from 6% at birth to 90% at 4½ months.

4. The absence of death *in utero* from sickle cell anemia may be due to the protective influence of fetal hemoglobin which is unable to sickle even at the low oxygen tension which exists in the fetus.

* Since this paper was submitted for publication, 11 infants with sicklemia have been followed for 4 months at monthly intervals since birth. Sickling increased progressively to reach an average of 90% at the age of 4 months.

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THE LEUKOCYTOSIS OF DIABETIC ACIDOSIS

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Leukocytosis is of common occurrence in diabetic acidosis.[1,2,3,7] It is generally polymorphonuclear in type. Allan[1,2] first pointed out that its occurrence is apparently independent of the presence or absence of intercurrent infection. Rather extreme leukocyte levels are sometimes seen. Root[8] reports a white count as high as 92,000 in diabetic coma, and Anderson[3] reports a white count of 97,000. Heck and Hall[6] state that diabetic acidosis is sometimes accompanied by a leukemoid reaction, with young leukocytes, myelocytes and even myeloblasts appearing in the peripheral circulation.

Working with experimental anisotonia in animals, it was recently shown[11] that a selective polymorphonuclear leukocytosis regularly accompanied the induction of extracellular hypertonicity. The increased concentration/mm.^{3} of absolute numbers of circulating neutrophils was roughly proportional to the increase in milliosmolar strength of the serum. The hypothesis was advanced that under certain conditions, hypertonicity of the extracellular fluids might be an important contributing factor for the production of polymorphonuclear leukocytosis.

It was the purpose of the present study to observe the levels of hypertonicity naturally occurring in the course of diabetic acidosis and see if they bore any relationship to the extent of leukocytosis which accompanied it.

Methods. Seven consecutive diabetic coma admissions to the New England Deaconess Hospital were studied. Levels of hypertonicity were determined by freezing point depression measurements on defibrinated blood samples and are reported in milliosmoles per liter.* Absolute neutrophil counts were determined by total white counts and concurrent differential counts on 500 cells. All white blood cell counts were previously corrected for hemoconcentration by observing the variation in hematocrit values between coma and recovery.

Levels of tonicity of the serum were recorded at the height of coma, 6 hours later, and following return to a "normal" status. Absolute neutrophil levels were recorded at the height of coma, 20 hours later and following return to a "normal" status.

Results. The data obtained is presented in tabular form in Table 1.

In each case a substantial level of hypertonicity was recorded during the height of coma. Similarly, a substantial level of leukocytosis was recorded during the height of coma. The increases in count were accompanied by a "shift to the left" in the Schilling hemogram, with immature polymorphs and, on two occasions, myelocytes appearing in the circulation. If one plots the absolute neutrophil counts obtained at the height of coma against the concurrent hypertonicity of the serum it will be seen that they bore a direct proportionality to one another (Fig. 1).

All points fell close enough to a straight line relationship to be within the range of experimental error, excepting one. In that instance an absolute neutrophil count of 20,000 was considerably higher than would have been anticipated from the molarity of the patient's serum alone. It is of interest that in that instance a concomitant infectional element may have been present as the patient was under observation for acute appendicitis. No correlation existed between the level of

* Conversion factor $\triangle T_f = 1{\cdot}86M$.

TABLE 1.—ANALYTICAL DATA

Analysis	Patient	Time: Coma	6 hrs. post coma	20 hrs. post coma	Return to normal*
Molarity milliosmoles /l.	V. L.	381	322	..	328
	M. H.	370	355	..	301
	P. McG.	392	370	..	339
	L. D.	344	322	306	306
	E. R.	355	..	..	322
	L. P.	360	..	..	306
	M. L.	406	..	..	349
W. B. C.	V. L.	26,760	..	9,760	..
	M. H.	19,080	..	5,680	..
	P. McG.	21,850	..	11,120	6,440
	L. D.	18,700	10,000	4,080	4,120
	E. R.	24,350	..	11,650	4,280
	L. P.	20,020	..	11,550	5,300
	M. L.	22,720	15,520	13,960	11,960

Smear		SEG.	STAB.	MYL.	E.	L.	M.	SEG.	STAB.	MYL.	E.	L.	M.	SEG.	STAB.	MYL.	E.	L.	M.	SEG.	STAB.	MYL.	E.	L.	M.
	V. L.	62	20	0	0	18	0	..	..	..	..	..	..	55	11	0	0	28	6	..	..	..	..	..	..
	M. H.	83	3	0	0	9	5	..	..	..	..	..	..	68	0	0	0	21	11	..	..	..	..	..	..
	P. McG.	80	6	3	0	9	2	..	..	..	..	..	..	78	2	1	0	11	8	54	0	0	1	40	5
	L. D.	71	12	0	0	14	3	72	13	0	0	12	3	68	15	0	0	16	2	51	3	0	0	44	3
	E. R.	81	8	2	0	8	1	..	..	..	..	..	..	74	6	1	1	16	2	52	0	0	3	40	5
	L. P.	80	14	0	0	4	1	..	..	..	..	..	..	79	5	0	0	6	10	76	0	0	0	19	5
	M. L.	82	5	0	0	13	0	82	1	0	0	16	1	80	1	0	0	12	7	..	..	..	..	..	..
Hematocrit vols. %	V. L.	55						..						46						44					
	M. H.	52						..						..						42					
	P. McG.	49						..						..						39					
	L. D.	51						..						..						37					
	E. R.	39						..						..						38					
	L. P.	44						..						..						37					
	M. L.	44						..						..						43					
CO_2 m M/l.	V. L.	5						7						19						..					
	M. H.	9						11						..						..					
	P. McG.	14						..						..						..					
	L. D.	4						..						..						..					
	E. R.	9						..						..						28					
	L. P.	5						..						20						..					
	M. L	5						7						14						..					
Bl. sugar mg. %	V. L.	728						185						56						77					
	M. H.	305						105						253						190					
	P. McG.	450						123						280						98					
	L. D.	353						233						115						256					
	E. R.	390						151						180						..					
	L. P.	445						250						172						203					
	M. L.	910						452						248						72					

* 1–3 weeks post coma

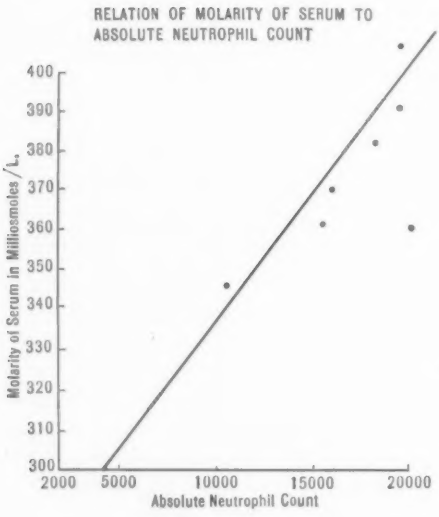

FIG. 1.

absolute neutrophil count and molarity of the serum, once the period of recovery ensued. In general, a relative leukopenia and neutropenia was common for a month or more after recovery from coma.

It is of interest that no eosinophils were seen in any blood smear during coma.

Discussion. Although a proportional fluctuation in the molarity of the serum and absolute numbers of circulating neutrophils does not, of itself, imply a cause and effect relationship, it would seem, in view of the previously reported experimental relationship,[11] and in view of the close proportionality observed in this series of cases, that such a possibility is worthy of consideration.

The exact mechanism of such a hypertonic-leukocytosis would remain to be defined, but would seem to be an effect of the hypertonicity *per se* rather than an effect of increased concentration of any one or more of the elements comprising the hypertonicity. The experimentally induced hypertonicity was essentially an increased concentration of Na^+ and Cl^-, whereas the reverse obtains in the hypertonicity of diabetic coma. As repeatedly shown by Sunderman,[9,10] Atchley, Loeb, *et al.*,[4] Danowski, Winkler and Peters[5] and others, there is a lowering of plasma Na^+ and Cl^- levels in diabetic acidosis. The hypertonicity of diabetic coma is essentially an increase in the organic constituents of the plasma: sugar, urea and ketone bodies. Thus, if the same process incites the leukocytosis in both instances it would imply an effect of the hypertonicity itself, rather than effect of the elements which comprise it.

Summary. Seven cases of diabetic acidosis are presented, in which studies were made on the simultaneous fluctuations in molarity of the serum and absolute numbers of circulating neutrophils.

The hypothesis is advanced that the hypertonicity of the plasma in diabetic acidosis may play a causative rôle in the concomitant leukocytosis.

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BENIGN IDIOPATHIC SPONTANEOUS PNEUMOTHORAX

A Review of 63 Cases*

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In 1943 the United States Army had 873 hospital admissions for simple benign idiopathic spontaneous pneumothorax.[4] In recent years it has become apparent that idiopathic spontaneous pneumothorax is relatively common. Kjaergaard[2] studied 51 cases admitted to the hospitals of Denmark in a 20 year period. Perry[6] found 85 cases in the London Hospital record in a 14 year period. Ornstein and Lercher[5] reported a study of 58 cases. Blackford[1] reviewed 15 cases in college students at the University of Virginia. Leach[3] reported 126 cases from the Army Air Forces. Niehaus[4] reported 24 cases.

Benign idiopathic spontaneous pneumothorax occurs most often in healthy young adult males. Pleural fluid is slight or absent. Fever is uncommon. Uncomplicated reëxpansion is the rule, but recurrence is not infrequent. The chest roentgenogram is negative for infiltration. The usual explanation for spontaneous pneumothorax is the rupture of alveolar walls with air dissecting its way along interstitial bands to the pleura, and causing the formation of a bleb. This bleb has a check valve, allowing the entrance, but not the egress of air, with resultant ballooning, thinning and rupture of the bleb. It is important that the benign nature of idiopathic spontaneous pneumothorax be recognized and that pulmonary tuberculosis not be incriminated.

This report, based on 63 cases, is a clinical study of 2 groups of patients, 1 group of 27 studied in Los Angeles, and the other group of 36 patients seen at Bellevue Hospital in New York. The material is best presented under several headings.

Age of Patient. The youngest patient was 18; the oldest was 62 years of age. Seventy-five % of patients were under 40 years of age, and almost 50% were between 20 and 30 years. Thus, benign spontaneous pneumothorax is primarily a disease of young adults (Table 1).

Table 1.—Age of 63 Patients With Spontaneous Pneumothorax

Age	No.
18–20	4
21–30	30
31–40	13
41–50	10
51–60	4
61–62	2

Sex. In the Los Angeles group only males were examined. In the Bellevue Hospital group there were 30 males (26 white, 4 colored), and 6 females (5 white and 1 colored). The ratio of males to females was 5 to 1.

Side of Pneumothorax. In most studies the spontaneous pneumothorax was more often on the right side. In our studies, 31 patients had a right pneumothorax and 32 a left. Right and left side appear to be affected equally.

Time for Reëxpansion (Table 2). In almost 70% of patients the time for reexpansion was 7 weeks or less. In the individual patient it was difficult to pre-

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TABLE 2.—TIME FOR REËXPANSION IN 57 CASES OF SPONTANEOUS PNEUMOTHORAX

Weeks	No.
1	3
2	3
3	8
4	8
5	8
6	6
7	9
8	7
9	1
10	1
11	0
Over 11	3

dict the time for reëxpansion. Leakage of air into the pleural space may continue for days, and even weeks. Of 3 patients who had 15% collapse, 1 required 26 days, the second 7 days, and the third 50 days for reëxpansion. One patient had a 50% collapse on admission with gradually increasing collapse to 90% in a period of 2 weeks, and then uncomplicated reëxpansion. Another patient "blew out" again on the 9th hospital day, and then had an uncomplicated reëxpansion. One patient required 100 days to reëxpand his collapsed lung. Air samples on the 56th hospital day were consistent with a diagnosis of bronchopleural fistula.

ETIOLOGY. Five patients gave a history of bronchial asthma. None, however, had an asthmatic attack at the time of the pneumothorax. In 58 patients the cause was not apparent and was therefore labeled idiopathic. It was noted that almost every patient was thin and underweight. Several patients were of normal weight. None was overweight or obese.

HISTORY OF EFFORT. In only 2 patients (3%) did the onset of symptoms occur during or just after effort. One patient had thrown a football, and another was straining at stool. Four patients were aroused from sleep. A history of effort associated with the onset of symptoms was rare, and apparently coincidental.

CHEST PAIN. Chest pain occurred in 62 patients, or almost 100% of cases. This pain was usually described as "sharp" and "cutting," rarely as "dull," and was always on the side of the pneumothorax. Frequently the pain was pleuritic and lasted from 1 to 4 days. Benign spontaneous pneumothorax may be completely asymptomatic. One patient had a right pneumothorax with sudden pain in 1938. On a routine clinic visit 1 year later she was found to have a 10% collapse of the right lung. She was completely asymptomatic. Two patients, not included in this series, also had asymptomatic spontaneous pneumothoraces. One patient was admitted with severe urticaria. On routine fluoroscopy she was found to have a spontaneous pneumothorax. Another patient had a transverse myelitis and persistent fever. A chest film showed 50% collapse of the right lung. Wilson[7] found 5 cases of spontaneous pneumothorax without symptoms on routine chest Roentgen rays of Yale students in a 4 year period.

DYSPNEA. Fifty-two patients (83%) had slight to marked dyspnea. It was difficult to correlate the degree of collapse with the severity of the dyspnea. One patient with 70% collapse and another with 60% collapse gave no history of dyspnea. One patient with almost 100% collapse of the left lung had moderate dyspnea, whereas 2 young adults with a 5% collapse also had moderate dyspnea. Several patients had increasing dyspnea during the first few days. As a group, however, the greater the degree of collapse, the more severe the dyspnea.

PLEURAL ADHESIONS. In benign idiopathic spontaneous pneumothorax, the chest roentgenogram reveals no infiltration either at time of lung collapse or when the lung is reëxpanded. In this study no patient had pleural adhesions demonstrable by chest roentgenogram. In Ornstein's group, the 3 patients who had adhesions developed active pulmonary tuberculosis within 3 years. Of 25 consecutive unselected patients admitted to the chest service of Bellevue Hospital with active pulmonary tuberculosis and a spontaneous pneumothorax, 24 had pleural adhesions demonstrable on Roentgen ray. The presence of adhesions with a spontaneous pneumothorax calls for careful clinical

study and continued observation for a possible tuberculous cause.

CYANOSIS. Five patients (8%) were slightly cyanotic at the onset. These patients had moderate to marked dyspnea, and 4 had over 50% lung collapse.

PLEURAL FLUID. Forty patients (65%) had no pleural fluid; 23 patients had pleural fluid, enough to blunt the costophrenic angle in 19, to the level of the diaphragm in 2, and above the diaphragm in 2. The 2 patients with fluid above the diaphragm had thoracenteses, and "pure blood" was aspirated. One patient continued to reaccumulate fluid which became more serous and then ceased after 6 weeks. After 3 years, this patient is in good health. In 25 unselected consecutive patients with active pulmonary tuberculosis and spontaneous pneumothoraces, 13 had fluid above the level of the diaphragm. In idiopathic spontaneous pneumothorax, the accumulation of appreciable amount of fluid, that is above the level of the diaphragm, is unusual, and in such cases the possibility of underlying pulmonary tuberculosis or other pulmonary disease must be considered.

SEDIMENTATION RATE. In 22 patients the sedimentation rate was normal. It was slightly elevated in 8 and was not determined in 35 patients, on admission. In benign idiopathic spontaneous pneumothorax a normal or slightly elevated sedimentation rate is usual.

LEUKOCYTE COUNT. On admission, 21 patients had normal white blood cell counts and 9 patients had slight to moderate elevation of the leukocyte count. These quickly returned to normal, unless there was another explanation for the leukocytosis. (The white blood cell count was not determined on the remaining patients on admission.)

FEVER. Seven patients had a low fever lasting 1 week or less. One patient had fever for 1 month, but he developed thrombophlebitis of the leg soon after admission. Another patient was afebrile for 3 weeks and then had fever for 2 weeks during which time he had clinical evidence of a leg thrombophlebitis. Ordinary uncomplicated cases of spontaneous pneumothorax were unaccompanied by fever lasting more than a few days. If fever persists, another explanation must be sought. If none is found, the spontaneous pneumothorax should not be regarded as benign.

TREATMENT. The patient is kept at bed rest until the collapsed lung has reëxpanded. Bathroom privileges are permitted when the lung has reëxpanded to about 80 or 85% of its volume. Following complete reëxpansion, the patient is allowed full activity and a return to normal life. In case of positive pressure pneumothorax, due to a ball-valve type of action, aspiration of air or temporary tidal drainage is indicated. No case in this series had this complication.

RECURRENCE. Nineteen % of patients had recurrent pneumothoraces. Ten of such patients had collapse of the same lung, and 2 had collapse of the opposite lung. Three patients had 1 recurrence, 5 had 2 recurrences, 2 had 3, 1 had 4, and 1 had 6 recurrences.

FOLLOW-UP. Eighteen patients had careful and adequate study with serial chest roentgenograms for from 1 to 8 years following their idiopathic spontaneous pneumothoraces. All were found to be in good health and none had any evidence of tuberculosis.

Summary. A clinical study of 63 patients with benign idiopathic spontaneous pneumothorax is presented. The following were noted: 1. Half of the patients were between 20 and 30 years of age. The ratio of males to females was 5 to 1.

2. Half of the pneumothoraces were on the right side and 50% on the left.

3. In 70% of patients the time for reexpansion was 7 weeks or less. In the individual patient it was difficult to predict the time required for reëxpansion.

4. In only 2 patients (3%) did physical exertion precede the onset of the spontaneous pneumothorax.

5. Chest pain occurred in 62 patients (almost 100%) and subsided in a few days.

6. Dyspnea was present in 52 patients (83%).

7. Five patients (8%) were slightly cyanotic at the onset.

8. Forty patients (65%) had no pleural fluid. Two patients had fluid above the diaphragm, and in both "gross blood" was aspirated.

9. No patient had pleural adhesions demonstrable on chest roentgenogram. This is in sharp contrast to a study of 25 patients with active pulmonary tuberculosis and spontaneous pneumothorax in whom 24 had demonstrable pleural adhesions, and 13 had fluid above the level of the diaphragm.

10. The sedimentation rate was normal in 73% of the group of patients in which this was performed, and slightly elevated in 27%.

11. Of those patients having white blood cell counts on admission, 70% were normal and 30% showed slight to moderate elevation.

12. Only 7 patients had a low fever lasting 1 week or less. The other patients were afebrile. Two patients had fever lasting more than 1 week, and both had thrombophlebitis of a leg.

13. Recurrences occurred in 19% of the patients, usually on the side of the previous collapse.

Conclusions. Benign idiopathic spontaneous pneumothorax occurs most often in young healthy adult males. Fever and elevation of the white blood cell count and sedimentation rate, if present, are slight and transient. Pleural adhesions and appreciable amounts of pleural fluid other than "gross blood" from pleural tears, are very unusual and should arouse the suspicion of underlying pulmonary tuberculosis or other disease of the lungs. The prognosis of benign idiopathic spontaneous pneumothorax is excellent and uncomplicated reëxpansion is the rule.

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PLEURITIC PAIN: USE OF INTRAVENOUS CALCIUM GLUCONATE IN ITS RELIEF

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It is usually stated in textbooks of medicine and physiology that the pain of pleurisy is due to friction between the inflamed pleural surfaces. This is based partly on the demonstration by Capps and Coleman[6] that the parietal pleura is sensitive to painful stimuli. Certain clinical observations on relief of pleuritic pain by various methods have indicated, however, that the mechanism of the pain is more complex than simple friction between the pleural surfaces. The purpose of the present report is to describe the relief of acute pleuritic pain by intravenous administration of calcium gluconate, and to discuss the significance of this and other observations in reference to the probable mechanism of the pain.

Method. The procedure consisted of the intravenous injection of 10 to 20 ml. of 10% calcium gluconate solution during a period of 2 to 4 minutes. The effect of this on pleuritic pain will be described in the next section. Two side-effects were noted: a sense of warmth and flushing, and occasional mild nausea. The drug was not used in patients receiving digitalis because of possible toxic reactions.[3,9] In order to rule out the possibility that the sense of warmth and flushing after calcium played a part in the results obtained, several patients were first given 100 mg. of nicotinic acid intravenously. This caused marked flushing of the skin, but had no effect on the pain.

Results. Thirty patients with acute pleuritic pain due either to pneumonia or pulmonary infarction were treated by injection of calcium gluconate. The results are summarized in the accompanying table. All but 3 of the patients experienced definite relief of pain. Of the 3 patients who were unrelieved, 2 were likewise unaffected by procain block of the intercostal nerves while the third experienced relief from that procedure.

Table 1.—Results of Intravenous Injections of Calcium Gluconate in 30 Patients With Acute Pleuritic Pain

Diagnosis	Pneumonia	Pulmonary infarction
Complete relief	4	0
Partial relief	20	3
No relief	1*	2
Total patients	25	5

* This patient obtained no relief of pain with intercostal nerve block.

In only 4 of the 27 patients who obtained relief with calcium gluconate did the pain disappear completely and not return. Usually there was a very marked, but not complete relief; this was evidenced by easier, fuller respirations and ability to cough. The effect was evident within 60 seconds after beginning of the injection. The residual pain was described by several patients as a dull aching, unrelated to respiratory movements. When the pain relief was not permanent, there was gradual return after a period of 30 to 60 minutes. Tenderness and hyperalgesia of the chest wall or upper abdominal muscles were also relieved by calcium only to reappear at the same time that the sharp pains on inspiration returned. In 10 patients, a second injection of calcium gluconate was again effective in ameliorat-

ing this pain. Most of the patients in this series were subsequently given more lasting relief by procain block of the intercostal nerves,[17] or by ethyl chloride spray.[7]

The practical value of the use of calcium injection lies in its simplicity. It enables the patient to cough and produce sputum, often of importance in determining the etiology of the pleurisy, and facilitates physical examination of the chest. Furthermore, as stated above, permanent relief of the pain occurs in some instances.

Discussion. In 1940, Buchthal and Clemmesen[4] reported electromyographic studies on patients with painful muscle spasm. They demonstrated that various drugs, among them calcium salts, brought about relaxation of the muscle spasm, evidenced both by palpable lessening of the spasm and by electromyographic changes. At the same time, pain was relieved. Other reports have emphasized the fact that calcium injection has a definite effect in the restoration of normal muscle tone.[1,14]

In 1928, Weiss and Davis[21] obtained relief of pain in pleurisy by injection of procain into the skin at the site of pain and tenderness. Relief was immediate, often complete and permanent. Occasionally, after several hours, the pain returned and a second injection was necessary. They noted in several patients that relief of pain in one area resulted in its appearance at another site. This too could be relieved by intracutaneous injection of procain. They offered the suggestion that normal impulses from the skin play upon a focus in the spinal cord made irritable by increased afferent impulses from the pleura, and these are interpreted as pain.

In 1939, Schnur[18] demonstrated that injection of procain directly into the pleural cavity at the site of maximum pain likewise afforded immediate and sometimes lasting relief.

Price[17] in 1943 reported the use of procain block of the intercostal nerves in pleurisy. He inferred that relief was due to block of the fibers carrying pain, and pointed out that often only one procain block gave permanent relief of pain, despite the fact that the duration of effect of this drug could not be more than a few hours.

In 1944, Kelly[12] pointed out similarities between chest pain associated with fibromyositis or muscular rheumatism and that accompanying the pleurisy of acute lung infections. Using the method of direct infiltration of the tender intercostal muscles with procain, he was able to obtain relief of pain in both types of disease. He concluded that the rôle played by abnormal sensitivity of the interrostal muscles in pleurisy was an important one perhaps of major significance in the causation of the pain.

Dybdahl[7] in 1944 described the relief of pleuritic pain by use of an ethyl chloride spray on the skin over the painful area. We also have been able to obtain striking relief with this procedure, many times complete and permanent. While Dybdahl recommended that a series of concentric frozen wheals be made at the site of pain, it has been our experience, as well as that of others employing the spray for other conditions,[2] that actual freezing of the skin is not necessary. The application of the spray for 20 to 30 seconds, producing only a transient cutaneous anesthesia is often all that is required.

The use of ethyl chloride as a spray for relief of pain was first suggested by Kraus[8] in 1935 as a rapid treatment of painful distortions of joints. In treating ankle-sprains, one application of the spray may give lasting relief, if active motion of the joint is begun immediately and is continued for a time.[13] Kraus suggested that momentary surface anesthesia in some way abolished painful muscle spasm and that continued active movement so restored the involved muscles to a normal or near normal state that spasm did not recur. Payr[16] in 1934 had described the so-called "chain" effect of painful muscle spasm. The chain consisted of sensory nerve, spinal cord, motor nerve, muscle and sensory nerve. Pain originating anywhere in the course of this chain leads to painful muscle spasm and the pain of the spasm

induces still more spasm and pain as the vicious cycle becomes established. If the chain can be broken at any point, the spasm is relieved and if the muscles can be restored to a more normal state during the pain-free interval (by active movement), the recurrence of spasm can be prevented.

That spasm of striated muscle can serve as primary source of pain was shown by Kabat and Knapp[11] who employed erythroidine for the relief of muscle spasm in acute anterior poliomyelitis. As spasm was relieved, pain disappeared. Wolff and his associates[19,20,22] in their extensive studies on pain mechanisms have demonstrated that certain types of headache are due to spasm of the muscles of the scalp and neck. McClellan and Goodell[15] pointed out the importance of abdominal muscle spasm in pain associated with disease of the urinary tract.

The relief of painful muscle spasm by curare has been demonstrated repeatedly.[10] This drug seems to have a selective action on hypertonic muscles, relieving spasticity with little effect on muscles of normal tone.[5] We have had occasion to use curare in 2 patients suffering from severe pleuritic pain due to lobar pneumonia and in both of them the pain was alleviated by this treatment.

The foregoing observations together with our results with intravenous calcium gluconate seem to indicate that a major portion of the pain associated with pleuritis is due to a painful spasm of the intercostal muscles which perpetuates itself in a vicious cycle of spasm, pain, and more spasm. Relief by any method seems to depend upon interruption of this cycle at some point.

Summary. Acute pleuritic pain was relieved in 27 of 30 patients by intravenous injection of calcium gluconate. This furnishes additional evidence that much of the pain of pleurisy is due to spasm of the intercostal muscles.

A "chain-theory" of painful muscle spasm as postulated by Payr would explain satisfactorily the relief of pleuritic pain by such varying methods as intracutaneous, intramuscular, and intrapleural injection of procain, intercostal nerve block, ethyl chloride spray, curare or intravenouscalcium gluconate.

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CENTRAL NERVOUS SYSTEM INVOLVEMENT DURING MUMPS

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There is abundant evidence that central nervous system involvement occurs frequently during infection with the virus of mumps.[29] That it may be a constant feature of this infection is not unlikely. It has been observed to precede, accompany or follow salivary gland swelling, and sometimes to present the only manifestation of mumps infection.[2,5,15,23,25] In most cases of mumps, symptoms of meningoencephalitis do not occur or are mild. The frequency with which it has been recognized clinically has varied widely.[29] However, examination of the spinal fluid during mumps has revealed abnormalities in a significant proportion of each series of cases in which routine lumbar punctures were made.[4,9,12,23,28] Experience would seem to indicate that involvement of the central nervous system during mumps is of little significance in the great majority of cases. Nevertheless, severe nervous system damage has been observed to occur.

It is the purpose of this report to present the manifestations of central nervous system involvement which were observed during the course of mumps in 77 consecutive cases in which lumbar punctures were done. The results of the study of 28 of these patients have been previously reported in brief.[14] A patient is described in whom disabling residual nervous system symptoms persisted.

Methods. Clinical observations and spinal fluid examinations were made on 77 consecutive cases of mumps which were observed in a U. S. Army General Hospital in England during the period November, 1942 to April, 1944. Most of the patients were young American soldiers. Thirteen were American civilians, the oldest of whom was 45. All were men. The diagnosis of mumps was supported by the presence of parotitis in all but one patient; he had epididymo-orchitis. In those without symptoms of meningoencephalitis, an initial lumbar puncture was usually done between the 8th and 12th day of illness. This time was chosen because it was believed that abnormalities were most likely to be discovered at this mid-period in the disease.[20,25,29] If clinical evidence suggestive of central nervous system involvement appeared, lumbar puncture was performed at that time. Patients whose spinal fluid was abnormal had subsequent lumbar punctures at 10-day intervals, in most cases, until the abnormality disappeared. Examination of spinal fluid was performed immediately after withdrawal. This included a total and differential cell count, qualitative test for increased globulin content by the method of Pandy and quantitative estimation of sugar and chlorides. Quantitative protein determinations were made on the fluid of 45 cases. The generally recognized normal range was used in evaluating the content of sugar, chlorides, and protein. Evidence of central nervous system involvement was not considered established unless a pleocytosis of 10 or more leukocytes per cu. mm. of spinal fluid was present.

Results. A summary of the incidence of central nervous system involvement

during mumps in this series is presented in Table 1. Certain pertinent findings in the 26 cases who had an increase in the number of leukocytes in the spinal fluid are tabu-

TABLE 1.—SUMMARY OF INCIDENCE OF CENTRAL NERVOUS SYSTEM INVOLVEMENT IN 77 CASES OF MUMPS*

Total number of patients	77
Number who had pleocytosis in spinal fluid	26(33.7%)
Cases with clinical evidence of meningoencephalitis	9(11.7%)
Number with pleocytosis in spinal fluid	8
Cases with no clinical evidence of meningoencephalitis	68
Number with pleocytosis in spinal fluid	18
Proportion of patients without signs who had pleocytosis	26.4%
Number of patients in whom epididymo-orchitis occurred	19(24.7%)
Number in this group whose spinal fluid showed pleocytosis	8
Proportion with epididymo-orchitis who had pleocytosis	42.1%
Number of patients with residual central nervous system sequelæ	1

* Pleocytosis (10 or more leukocytes per c.mm. of spinal fluid) was arbitrarily regarded as the requirement for evidence of central nervous system involvement.

lated in Table 2. Nine (11.7%) of the total of 77 patients had symptoms suggestive of meningoencephalitis and 8 of these showed pleocytosis in the spinal fluid. The other 68 patients had no clinical evidence of meningoencephalitis, but 18 (26.4%) of them had increased spinal fluid cell counts. Pleocytosis in the spinal fluid occurred more frequently in patients who also developed epididymo-orchitis, 8 or 42.1% of 19 cases. There was no correlation between the number of cells and clinical evidence of central nervous system involvement.

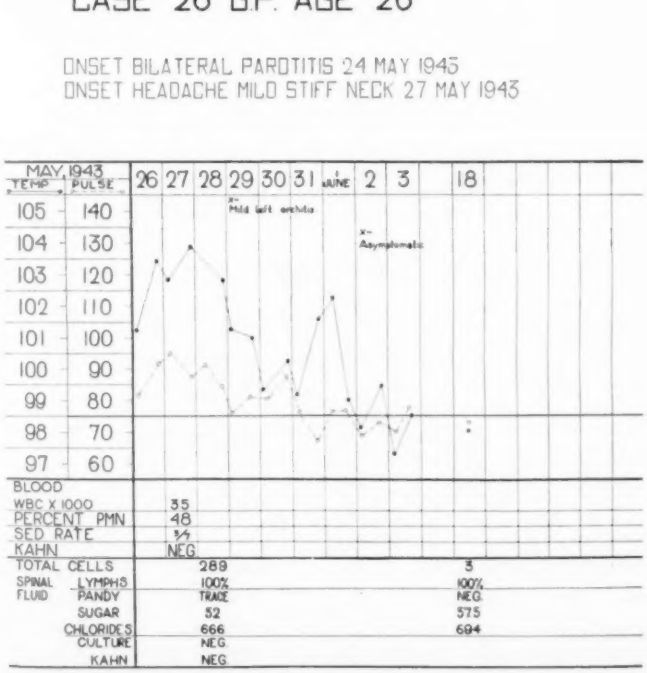

FIG. 1.—The course of a patient with mild symptoms of meningoencephalitis and pleocytosis in spinal fluid.

TABLE 2.—SUMMARY OF 26 PATIENTS WITH EVIDENCE OF CENTRAL NERVOUS SYSTEM INVOLVEMENT DURING MUMPS*

		Manifestations of mumps					Central nervous system manifestations								
					Temperature		Clinical			Spinal fluid					
Case	Age	Parotitis	Epididymo-orchitis	Max. leukocyte count (× 1000)	Maximum	Day of disease	Headache	Stiff neck	Others	Total cells/c.mm.	Total lymphocytes	Pandy	Protein (mg./100 cc.)	Day examined	Days in hospital
A. S.	22	Bilat.	None	7.0	104	5	Mild	Mild	Nausea	44	41	+	Not done	5th	41
										20	20	0		15th	
										18	18	0		25th	
J. G.	26	Bilat.	Unilat.	6.0	102.6	9	Mild	None	None	213	213	+	"	10th	32
										19	10	0		20th	
										4	1	0		30th	
R. C.	29	Bilat.	None	4.0	103	7	None	None	None	36	32	+	"	8th	38
										17	13	0		13th	
										7	7	0		26th	
W. C.	22	Bilat.	Unilat.	6.0	100	5	None	None	None	35	27	0	"	12th	30
										9	8	0		28th	
C. T.	21	Bilat.	Unilat.	11.0	105	5	None	None	None	37	33	0	"	10th	42
										14	13	+		21st	
										9	8	+		31st	
J. M.	34	Unilat.	None	7.0	99	2	None	None	None	95	86	0	"	12th	25
										4	3	+		21st	
C. C.	33	Bilat.	Unilat.	10.0	104	5	None	None	None	47	39	+	"	13th	53
										16	16	+		23rd	
D. M.	22	Bilat.	None	3.25	98.6	..	None	None	None	10	10	0	"	10th	28
										0	0	0		20th	
C. D.	28	Bilat.	Unilat.	7.05	103	8	None	None	None	85	83	+	"	9th	38
										4	3	0		26th	
F. D.	34	Unilat.	None	4.05	101	13	None	None	None	372	342	0	"	14th	39
										40	36	0		24th	
										6	5	0		36th	
W. P.	23	Bilat.	Unilat.	13.0	105	6	None	None	None	33	25	+	"	14th	39
										18	15	0		27th	
										1	1	0		36th	
H. T.	26	Bilat.	None	5.95	103	4	None	None	None	67	66	+	"	12th	31
										12	12	+		25th	
T. J.	22	Bilat.	None	4.8	99.4	1	None	None	None	16	16	0	"	10th	21
G. P.	26	Bilat.	Unilat.	3.5	104	3	Mod.	Mod.	Kernig pos.	289	289	+	"	4th	28
										3	3	−		25th	
H. H.	23	Bilat.	None	6.0	102	1	None	None	None	83	66	0	"	8th	29
W. K.	28	Unilat.	None	3.85	102.6	7	Mod.	Mod.	Nausea	262	229	+	..	5th	37
										15	13	+	70	15th	
										7	7	0	42	26th	
J. L.	23	Unilat.	None	4.9	98.6	..	None	None	None	29	29	0	..	9th	27
										3	3	0	20	19th	
E. H.	22	Bilat.	None	6.0	103.6	6	Mod.	None	Vomiting	210	185	+	69	6th	37
										18	18	+	47	21st	
										16	16	0	37	31st	
D. S.	23	Bilat.	None	5.5	103	6	None	None	None	41	35	0	60	10th	33
										9	9	+	100	21st	
W. S.	30	Bilat.	None	5.0	102.2	7	Mod.	None	Vomiting	15	13	0	37	12th	21
S. K.	25	Bilat.	None	5.6	..	..	Severe	Mild	None	190	182	+	82	6th	30
										17	16	0	34	19th	
C. H.	24	None	Bilat.	16.8	106	3	Severe	Mod.	Irrational	170	150	+	30	3rd	12
									Residual	24	18	0	45	23rd	mos.
									Disability	4	4	0	35	41st	
F. B.	40	Bilat.	None	7.2	102.2	6	None	None	None	200	180	0	49	11th	32
										3	3	0	..	25th	
W. L.	20	Bilat.	None	5.4	99.6	1	None	None	None	22	10	0	40	10th	21
R. R.	20	Unilat.	None	6.05	100	5	None	None	None	17	7	0	38	9th	21
C. B.	22	Bilat.	None	5.0	102	9	None	None	None	293	280	0	40	13th	31
										11	9	0	30	27th	

* Only cases with 10 or more leukocytes per c.mm. of spinal fluid are listed.

The chloride and sugar content of the spinal fluid was normal in all patients and showed no significant change when other abnormalities were present. In the 45 patients in which total protein was measured, it was over 50 mg. per 100 cc. in only 4 of the 11 who also had pleocytosis. There was no correlation between the level obtained and the degree of pleocytosis. The spinal fluid of 9 other patients had amounts of protein over 50 mg. per 100 cc. without increase in total leukocytes or

symptoms suggestive of meningoencephalitis. The values obtained were 77, 54, 120, 56, 53, 58, 102, 54, and 75 mg. per 100 cc. The significance of this isolated finding is not emphasized and the cases in which it was observed were not included in tabulating the incidence of central nervous system involvement in this series. The addition of these 9 cases to the list of those with evidence of meningoencephalitis

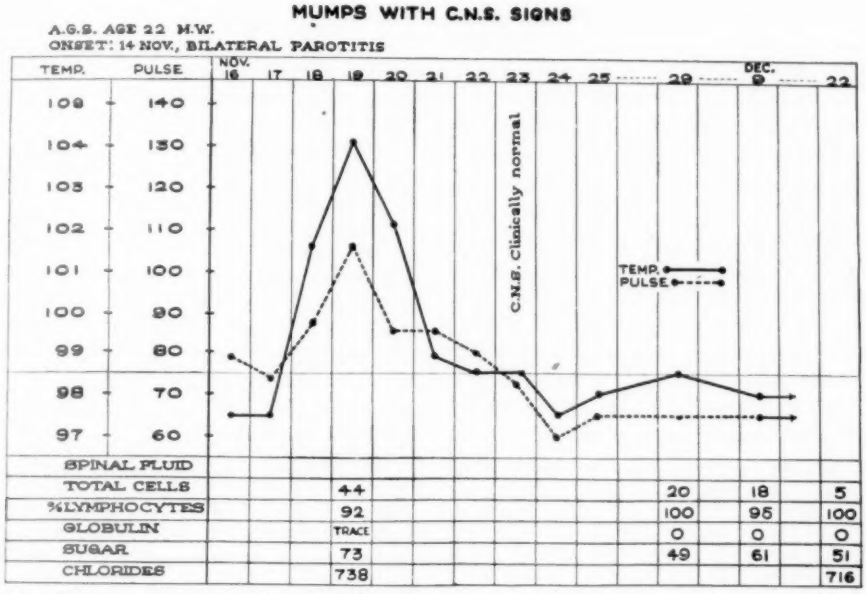

FIG. 2.—The course of a patient with moderately pronounced symptoms of meningoencephalitis and 44 leukocytes per c.mm. of spinal fluid.

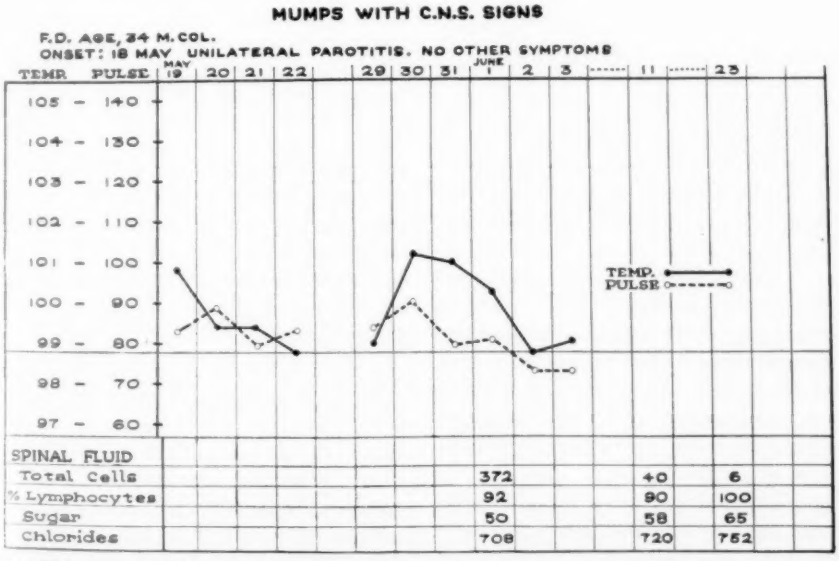
MUMPS WITH C.N.S. SIGNS
F.D. AGE, 34 M. COL.
ONSET: 18 MAY UNILATERAL PAROTITIS. NO OTHER SYMPTOMS
TEMP. PULSE
MAY 19 20 21 22 29 30 31 JUNE 1 2 3 11 23
TEMP.
PULSE
SPINAL FLUID
Total Cells 372 40 6
% Lymphocytes 92 90 100
Sugar 50 58 65
Chlorides 708 720 752

FIG. 3.—This patient had no clinical evidence of central nervous system involvement. His spinal fluid contained the greatest number of leukocytes of any in the series.

increases the incidence to 35 (45.5%) of a total of 77 examined.

The clinical evidence of meningoencephalitis observed in 9 cases included headache, stiff neck, nausea, vomiting and vertigo, one or more in varying degree in each patient. Except for 1 patient, to be described, the symptoms were mild and cleared rapidly. Relief of headache and nausea occurred after lumbar puncture in nearly every instance. No significant neurological signs were observed. Figures 1, 2, and 3 present the clinical course and the findings in 3 patients. The case represented in Figure 1 had bilateral parotitis followed by mild stiff neck and headache, and the spinal fluid was abnormal. The one represented by Figure 2 had similar symptoms and signs, but with more severe headache, stiff neck, and nausea. Fever and other symptoms disappeared rapidly after lumbar puncture. The patient in Figure 3 had mild unilateral parotitis, mild constitutional reaction and no symptoms referable to the central nervous system. His spinal fluid contained the greatest number of cells.

The data on patients with pleocytosis in the spinal fluid are listed in Table 2. In general, the degree of pleocytosis diminished rapidly within a few days but this was variable. The number of days in hospital for each patient is indicated. The duration of hospitalization was dependent upon the disappearance of abnormalities in the spinal fluid. Symptoms disappeared early. The patients were kept at nearly complete bed rest while abnormalities were present. It seemed reasonable to regard these changes, even though slight, as evidence of the presence of diffuse central nervous system involvement. The patients in whom the spinal fluid was normal were permitted activity when clinical signs of mumps had subsided and were discharged on the 20–21st day, in keeping with the policy of quarantine.

One patient of the series has remained seriously disabled following acute meningoencephalitis. His course will be described in some detail.

Case Report. The patient, a 24 year old white male, was well until October 3, 1943. On this day he developed mild sore throat and fever which was thought to be due to pharyngitis, endemic in the region at the time. The fever continued and he was admitted to the hospital on October 5. On this day the temperature rose to 105° F., the next day to 106° F. and the patient became irrational. Swelling of both testes was noted on this day. Examination revealed the patient to be flushed and irrational. He lay on his side, knees drawn up, head slightly retracted and neck moderately stiff. The pharynx was slightly reddened. The fundi and external ocular movements appeared normal. There was no enlargement of the salivary glands. Both testes were very tender and twice normal in size. The abdominal reflexes were equal and active. The right patellar jerk was diminished and the right ankle jerk was absent. There was an abnormal plantar response, not a typical Babinski sign, on the right. The total leukocyte count in the blood was 16,800 per cu. mm.; P.M.N. 68%, lymphocytes 20%, monocytes 10%. Urinalysis was normal. The spinal fluid revealed: 170 leukocytes per cu. mm., 80% lymphocytes; total protein: 30 mg. per 100 cc.; Pandy test: trace, chlorides 659 mg. per 100 cc.; Gold curve: 0001110000. Blood and spinal fluid Kahn tests were negative. The initial impression was acute epididymo-orchitis and meningoencephalitis due to mumps. During the next 4 days the temperature gradually became normal and remained so. The patient slowly became rational. After 2 weeks the mental confusion had improved but was still present. Swelling of the testes disappeared in 1 week. By October 24 he was coöperative but slightly confused, euphoric but with lability of mood. Occasional uncontrollable tremor occurred of the right arm and head, especially when upset. His voice was harsh and hard to understand. Visualization of the larynx revealed general atony with incomplete paresis of the adductor muscles. The gag reflex was absent. There was difficulty in reading fine print, vision 20/60 J4 in both eyes. Pupils were equal and reacted normally. Hearing was normal. There was marked ataxia with mild asterognosis and adiadochokinesia. The left patellar reflex was slightly more active than the right. Other reflexes, including abdominal and

cremasteric, were equal and active. General muscle power was diminished symmetrically. The testes appeared normal.

After 2 months the patient's judgment became more acute and euphoria diminished to be replaced by occasional episodes of depression. Speech was clearer and tremor of the right arm and head had disappeared. He was able to stand and take a few steps unaided, but ataxia remained marked. Vertigo was present on standing. Vision was not improved, the gag reflex remained absent and atony of the larynx persisted. Deep and superficial reflexes were equal and active. The right plantar response remained abnormal but did not represent a typical Babinski sign.

The total and differential blood count was normal on October 26 and subsequently. There was no anemia. Spinal fluid examination of October 26 revealed 24 cells, 75% of which were lymphocytes; total protein, 45 mg. per 100 cc., Pandy test negative; sugar, 66 mg. per 100 cc., chlorides, 698 mg.; Gold curve, 0000000000. The spinal fluid on November 13 was normal.

The family and past history was noncontributory. He had not previously had mumps. One contact developed typical mumps 2 weeks after onset of this patient's acute illness.

The patient was seen last on January 1, 1944. At that time his condition was as described above. In a letter, received in April, 1947, the patient indicated that improvement had taken place slowly in the 3-year interval, but that considerable residual disability remained.

In summary, this patient suffered from acute meningoencephalitis which occurred during the course of bilateral acute epididymo-orchitis, which was probably due to mumps. Specific antibody studies were not made. The possibility that the encephalitis was caused by an unknown intercurrent virus cannot be eliminated. Manifestations of severe central nervous system damage, with slight tendency to improvement, have persisted for at least 3½ years since the acute episode. This case is presented in some detail because of the likelihood that mumps was the cause of the serious central nervous system damage which resulted.

Discussion. Many studies have demonstrated that meningoencephalitis is a feature of mumps.[4,9,12,17,20,23,25,27,28] The present report supplies an additional series of patients in which clinical and spinal fluid examinations indicated the presence of central nervous system involvement in a significant proportion. It seems reasonable to believe that every patient with mumps is subject to the neurotropic effects of this virus. The frequency and character of the manifestations of this involvement must depend upon unknown individual factors. Enders and his colleagues have developed serologic and intradermal tests which have made possible specific diagnosis of infection with the virus of mumps.[8] The use of these methods has demonstrated that acute aseptic meningoencephalitis is frequently due to this specific agent.[8,13,24]

The clinical significance of the neurotropic activity of the mumps virus is not clear. In the great majority of cases of mumps only minor manifestations of encephalitis have been discovered. These cases are not followed by demonstrable central nervous system injury. However, severe encephalitis with residual disability due to nervous system damage sometimes occurs. Cases of this kind are unusual but numerous instances are on record.[6,7,11,16,17,18,20] Fatalities have been recorded. In a review of the literature Donohue found 10 cases in which histologic studies of the nervous system had been made; 7 of these were considered doubtful or inadequately studied.[7] He reported one additional case. The morphologic changes in the remaining 4 cases were variable but resembled those associated with post-infection encephalitis following many diseases. The view that severe encephalitis which sometimes develops during mumps is due to the activation of an unknown latent virus is widely expressed.[7,20,21,29] This is a reasonable hypothesis but is based upon circumstantial evidence. Globus,[10] after a comprehensive study concludes: "By placing side by side the various forms of inflammatory diseases of the central nervous system, a striking confluency of all the encephalitis

forms has been revealed, and it has been suggested that the minor histological differences express mainly the degree rather than the character of the pathologic process, and it is not unlikely that we are dealing here with variations in intensity of the excitant and variations in local vulnerability of the tissue rather than with the distinct types of causative agents." In recent years, studies of encephalitis due to different specific viruses have demonstrated that morphologic changes are variable. Since the mumps virus exhibits a definite neurotropic tendency it seems reasonable to suspect that it may occasionally be the primary specific cause of severe encephalitis. The sequence of events in the case reported in this paper suggested that all of the manifestations were due to the same agent. The question of the cause of encephalitis which occurs during many infections, including mumps, remains unsettled. The use of techniques now available will help to clarify the problem. In the management of patients it would appear sensible to regard any manifestation of encephalitis during mumps with some concern.

Many infections may be accompanied rarely by severe central nervous system involvement.[3,10,19,21,22,26,30] This is usually classified as post-infectious encephalitis. However, manifestations do not always follow the primary disease but sometimes make their appearance beforehand.[1] Of the exanthemata, measles is most frequently complicated by encephalitis.

There is a growing realization that invasion of the central nervous system, without clinical evidence of this involvement, may be a regular feature of many infections. For this reason the spinal fluid of 6 consecutive adult patients with measles was examined at the same time and under the same conditions as those in the study of mumps. Lumbar punctures were made between the 6th and 12th day of the disease. The spinal fluid cell counts were as follows: 26, 14, 11, 2, 1 and 0 cells/cu. mm. The patient whose spinal fluid contained 26 cells/cu. mm. had nausea, vomiting, slight confusion and mild stiff neck. The other patients had no clinical evidence of central nervous system involvement.

Study of the spinal fluid during infections is the simplest available means of investigating the presence of central nervous system involvement. The information obtained is limited but helpful. Studies similar to those reported are needed to determine the importance of the neurotropic effects of many infections.

Summary. The incidence and characteristics of central nervous system involvement was studied in 77 consecutive cases of mumps in which spinal fluid examinations were made. Pleocytosis (10 or more cells per cu. mm.) was present in the spinal fluid of 26 (33.7%). Clinical manifestations of meningoencephalitis were recognized in 9 cases. These were mild in all but 1 patient. The course of this patient is described. He suffered disabling residual nervous system damage which has persisted for $3\frac{1}{2}$ years. The problem of encephalitis which occasionally accompanies infectious diseases is briefly considered.

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HORMONAL HYPERTENSION AND NEPHROSCLEROSIS AS INFLUENCED BY THE DIET*

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It is now a firmly established fact that the treatment of rats with lyophilized anterior-pituitary (LAP) leads, under certain experimental conditions, to characteristic renal and cardiovascular lesions[12,13,14,16] which are similar to those produced by desoxycorticosterone acetate (DCA) or various chronic non-specific stresses. The histologic changes have been previously described:[11,15] the renal lesions are mainly characterized by enlargement and hyalinization of the glomeruli, formation of hyaline casts, dilatation of the renal tubules and thickening and hyaline necrosis of arteriolar walls. These pathologic modifications are considered to be similar to those described in the malignant ype of arterial hypertension. This condition will be referred to as *nephrosclerosis*.

Previous work shows that a marked hypertension is part of the syndrome produced by DCA overdosage or chronic non-specific stress.[11,15] Therefore we felt it important to determine whether the LAP nephrosclerosis would also be accompanied by elevation of the blood pressure. Furthermore, since it is known that a high protein diet is indispensable for the development of LAP nephrosclerosis,[6] we considered it pertinent to investigate whether it would also be essential for the production of hypertension. Secondly, as it has been found that rats receiving a diet deficient in the heat-stable fraction of the vitamin-B complex develop an increased blood pressure[2,3] and that the kidney lesions produced solely by high protein diets may be favorably influenced by addition of vitamins to the ration (see 3 for the pertinent literature), we also studied the possible protective effect of a few vitamins of the B-complex against the LAP nephrosclerosis and hypertension.

In the work described below we shall attempt to show that the LAP-nephrosclerosis is accompanied by hypertension, and that a low casein diet is effective both in preventing the histological lesions and the elevation of the blood pressure. We also present some evidence showing that an excessive amount of choline chloride tends to diminish the observed hypertension.

Methods. Nephrosclerosis was produced by a method previously published.[7] The procedure consists in the subcutaneous administration twice daily, of 10 to 15 mg. of lyophilized anterior-pituitary, to unilaterally nephrectomized castrated male rats (B.W. 40-80 gm.). If the animals are simultaneously given a 30%-casein, high-NaCl diet[6] beginning nephrosclerosis is obtained at the end of 21 days in almost all the rats.

The blood pressure was estimated by the direct method; a small needle washed in heparin, and connected with an open mercury manometer, was inserted into one

* A verbal preliminary account reporting on part of this work appeared in Federation Proc., **6**, 182, 1947.

of the carotid arteries and the pressure read as soon as the mercury level became constant. The determination was always performed under ether anesthesia. In order to avoid undue bleeding of the animal, the mercury level in the manometer was previously elevated to the expected value of the blood pressure.

The basic partially synthetic diets used throughout this investigation have already been described in detail[6] and had the following composition (Table 1):

TABLE 1.—COMPOSITION OF TWO BASIC SYNTHETIC DIETS (PARTS, PER CENT)

	Diet 1	Diet 2	Supplements	
Casein	30	15	1. Thiamine chloride	0.8 mg./100 gm. diet
Corn starch	59	74	2. Riboflavin	0.8 mg./100 gm. diet
Fat	1	1	3. Pyridoxine	0.8 mg./100 gm. diet
Cod liver oil	1	1	4. Ca pantothenate	4.0 mg./100 gm. diet
Bulk	1	1	5. Nicotinic acid	1.0 mg./100 gm. diet
Sodium chloride	4	4	6. Choline chloride	100.0 mg./100 gm. diet
Mineral mixture	4	4	7. Tocopherol acetate	10.0 mg./rat/weekly

The major difference between the 2 diets consists in a decrease of the casein content from 30% in Diet 1, to 15% in Diet 2. The corresponding increase in the carbohydrate percentage in Diet 2, has been shown not to exert any influence upon the incidence and severity of nephrosclerosis.[6] Except for the high proportion of sodium chloride, which is well tolerated, these 2 diets are fairly close to optimal.

The B-vitamins were supplied in the amounts indicated in Table 1; we will subsequently refer to such concentrations as the "normal amount" of vitamins. When we say, for example, that 10 times the normal amount of choline chloride was added to the diet, we mean that instead of the 100 mg. of choline chloride per 100 gm. of diet, 1000 mg. per 100 gm. of ration were used. The same applies to the other factors studied.

Experiments and Results. DIETARY PROTEIN AND HYPERTENSION. Two groups of 10 castrated male unilaterally nephrectomized, black and white rats, whose body weight ranged between 45 to 60 gm., were given a 30% casein diet (Diet 1). Group 1 received 20 mg. of LAP, suspended in 10% alcohol, in 2 daily subcutaneous injections, during 3 weeks. Group 2, acted as control and received no LAP. Two other similar groups of rats (Groups 3 and 4), were treated as Groups 1 and 2 respectively, but were fed a 15% casein diet (Diet 2) during the experimental period. At the end of 21 days the blood pressure was determined, and the animals were autopsied. The incidence and severity of the nephrosclerosis was

TABLE 2.—EFFECT OF THE CASEIN CONTENT OF THE DIET ON THE HYPERTENSION PRODUCED BY LAP* (AVERAGES AND STANDARD ERRORS)†

Groups	No. rats	Diets‡	Dose of LAP (mg./daily)	Final body wt.	Adrenal weight (mg.)	Kidney wt. mg./100 cm. of body surface	Nephrosclerosis: Incidence (%)	Nephrosclerosis: Severity (%)	Blood pressure (mm. Hg§)	Blood pressure: Percentage of hypertensive animals
1	19	30% Casein	..	126 ± 3.0	28.3 ± 0.7	455 ± 10	0	0	123 ± 1.8 (18)	0
2	36	30% Casein	20	163 ± 3.0	64.2 ± 1.6	858 ± 49	88	63	145.4 ¶ (24)	66
3	17	15% Casein	..	114 ± 3.2	25.0 ± 1.3	379 ± 12	0	0	113 ± 1.6	0
4	27	15% Casein	20	154 ± 3.6	41.9 ± 1.3	491 ± 51	11	11	108 ± 4.1 (14)	0

* Lyophilised anterior pituitary.

† The standard errors cited in this and subsequent Tables were calculated by the equation:

$$\text{S.E.M} \quad \sqrt{\frac{\Sigma d^2}{n\,(n-1)}} \qquad \sqrt{\frac{\Sigma d^2}{n\,(n-1)}}$$

‡ Diets 1 and 2.

§ Figures in parentheses refer to number of determinations.

¶ Hypertensive average 157 ± 4 mm. Hg.

calculated as previously described.[7] The weight of the adrenals and kidneys was determined after fixation in "Suza" mixture for 24 hours. Subsequently the renal lesions were also histologically evaluated, and expressed as a percentage of the maximum possible.

The first experiment was repeated 4 times, but in the last 2 instances, the groups not receiving LAP were omitted. As the results were essentially the same, they are summarized conjointly in Table 2. The number of rats refers to those surviving at the end of the experiments.

Table 2 confirms the previously observed fact,[6] that the composition of the diet is an essential factor for the production of nephrosclerosis by anterior-pituitary overdosage. While in the 15% casein group the incidence and severity of the renal lesions was very low, in the 30% casein group the incidence was 88% and the severity of the nephrosclerosis, 63%. In the control groups, not treated with LAP, the kidneys were entirely normal. Moreover, according to our expectation, the blood pressure in the 30%, LAP treated rats, was far above the normal average* and the rise statistically significant ($P = <0.01$). The value 145 ± 4 (standard error) mm. Hg is not, however, a true figure because it is composed of 16 hypertensive plus 8 normotensive rats. The hypertensive average (average of the 16 blood pressures higher than 135 mm. Hg) is 157 ± 4 mm. Hg which indicates, beyond any doubt, that the LAP nephrosclerosis is accompanied by a pronounced degree of hypertension. In this connection it is, however, indispensable to recall two facts: first, the direct method gives only the mean pressure which is much lower than the systolic; second, the observed elevation of the blood pressure was induced in a rather short period of time.

The second striking fact observed was that among the LAP-treated rats, those on 30% casein revealed a rather high incidence of hypertension while in the 15% casein group the blood pressure remained low.

In our opinion these observations conclusively demonstrate that below a minimum protein content (about 15%) LAP hypertension and nephrosclerosis cannot be obtained, at least under our experimental conditions.

Unexpectedly the comparison of the average blood pressure within the control groups, one receiving the 15% casein and the other the 30% protein ration, also reveals a statistically significant difference between both. Subsequently we proved that this difference had been due to the unilateral nephrectomy; intact animals treated with the same diets failed to present any difference between their blood pressures.

The differences in kidney and adrenal weights confirm our previous findings.[6] However, we want to emphasize the considerable difference in adrenal weight between Groups 2 and 4. It is statistically significant when calculated either in absolute terms or as a function of body weight. We believe that the parallelism between this pronounced adrenal enlargement and hormonal hypertension, is particularly noteworthy.

Regarding the effect of diet alone on suprarenal weight, we wish to emphasize that in rats fed a 15% protein ration the adrenal weight was 25.0 ± 1.3 (standard error) mg.; on the other hand, in the animals given a 30% casein diet the adrenal weight was 28.3 ± 0.7 (standard error) mg. The significance of this difference is dubious and if the adrenal weights are calculated as mg. per 100 gm. of body weight, the difference is not significant.

RELATION OF THE B-VITAMINS, TO HYPERTENSION AND NEPHROSCLEROSIS. In order to evaluate the possible rôle of the B-vitamins in our experimental hypertension and nephrosclerosis we first investigated the effect of the addition to the

* The mean blood pressure in the control rats receiving Diet 1 was 123 ± 7 (standard deviation) mm. Hg; therefore, a blood pressure of 123 ± 14 mm. Hg (20) should include 95% of the normal distribution, hence we felt justified in regarding 135 mm. Hg as the approximate highest limit of normal pressure.

diet of 10 times the "normal" amount of the B-vitamin mixture employed. As a small beneficial effect could be observed in this preliminary experiment, we repeated it twice more and in subsequent work we decided to find out if the protective effect would have been due to the vitamin mixture as a whole or to an individual factor only. To elucidate this point we planned some experiments in which the 30% casein diet was supplemented with 10 times the "normal" amount of each factor individually in addition to the "normal" amount of the whole vitamin mixture. As among the 6 B-vitamins so investigated only choline chloride† seemed to be beneficial, this observation was also repeated 2 more times. Each group of rats consisted of 10 animals treated exactly as in the experiments previously described; with the difference that the diet was supplemented as indicated in Table 3. In this table only the groups which were fed the diets containing 10 times the "normal" amount of all the vitamins and the ones containing 10 times the "normal" amount of choline chloride are tabulated. The results pertinent to the other 5 vitamins (thiamine, riboflavin, pyridoxine, calcium pantothenate, and nicotinic acid) are not listed because they were essentially negative. The groups treated with 30% casein but with "normal" vitamin supplements, are included in Table 3, for comparative purposes. Table 3 shows that the addition

TABLE 3.—EFFECT OF THE VITAMIN CONTENT OF THE DIET ON THE HYPERTENSION PRODUCED BY LAP* (AVERAGES AND STANDARD ERRORS)

Groups	No. rats	Diet†	Dose of LAP (mg./daily)	Final body weight	Adrenal weight (mg.)	Kidney wt. mg./100 cm. of body surface	Nephrosclerosis		Blood pressure	
							Incidence (%)	Severity (%)	(mm. Hg‡)	Percentage of hypertensive animals
1	27	30% Casein 10 × Vits.	20	156 ± 3.0	59.3 ± 1.8	900 ± 47	85	57	130 ± 3 (12)	33
2	36	30% Casein	20	163 ± 3.0	64.2 ± 1.6	858 ± 49	88	63	145 ± 4 (24)	66
3	27	30% Casein 10 × Choline chloride	20	163 ± 3.2	59.0 ± 1.7	731 ± 25	75	33	126 ± 2 (26)	15

* Lyophilized anterior pituitary.
† Diets 1 and 2 plus indicated supplementation.
‡ Figures in parentheses represent number of determinations.
§ Hypertensive average 157 ± 4 mm. Hg.

of 10 times the normal amount of the vitamin mixture or of choline chloride to the diet produced a significant decrease in the hypertension. We do not attach much importance to this observation, however, because the amelioration of the kidney lesions was practically none. We believe that more work has to be performed before concluding that choline chloride is effective in this type of hormonal hypertension and nephrosclerosis.

Discussion. For the reasons outlined in the introduction of this paper, the observed concomitant development of LAP-nephrosclerosis with high blood pressure was to be expected and, in our opinion, it represents further evidence that the anterior pituitary hormones may play a rôle in the pathogenesis of arterial hypertension. This laboratory has repeatedly defended the idea that nonspecific stress, acting on the anterior lobe of the hypophysis through an unknown mechanism may be one of the stimuli which ultimately lead to a malignant type of hypertension. This aspect of the question has been recently reviewed in detail, emphasizing the central position of the hypophysis in the pathogenesis of arterial

† The classification of choline chloride among the B-vitamins has been judiciously criticized by E. W. McHenry and J. M. Patterson: Physiol. Rev., **24**, 128–167, 1944.

hypertension in particular and of the "diseases of adaptation" in general.[14,16]

On the other hand, the part played by the adrenal glands in the pathogenesis of LAP-nephrosclerosis has been firmly established, since this condition cannot be obtained in adrenalectomized animals.[5]

The results presented in this communication point to the diet as one important factor in the genesis of this type of hypertension but we feel that its contribution is rather secondary as compared to the importance of the hypophyseo-adrenal system. In fact, we are particularly impressed by the observation that in the high protein groups the adrenals were markedly enlarged when compared with the corresponding glands of the low protein groups. It is probable that the diet merely accentuates the corticotrophic action of LAP or increases endogenous mineralocorticoid production to the hypertension-producing threshold, although available data does not permit one to favor any one of these assumptions.

Experiments now under way show that the hypertension produced by DCA is not influenced by the diet in the same drastic manner as the LAP hypertension; animals receiving large doses of DCA develop nephrosclerosis and hypertension of almost equal intensity on diets containing 15% or 30% casein. This seems to indicate that the part played by the high-protein diet in the LAP hypertension is predominantly, as we previously stated, to permit a pronounced enlargement of the suprarenal gland.

The effect of dietary protein alone on adrenal weight has been investigated by different investigators. While Tepperman, Engel and Long[17] claimed to have found an increase in adrenal weight on a high protein ration, Benua and Howard[1] and Ingle, Ginther and Nezamis[8] described negative findings and Leathem[9] first obtained no change and subsequently,[10] a barely significant increase. Our own results are also inconclusive except under LAP treatment, when the difference was always striking.

We do not believe that the results obtained with choline chloride indicate any relationship between our condition and the kidney lesions produced by choline deficiency. It has been established that 1 to 2 mg. per day of choline chloride prevents the hemorrhagic kidney[4] and even should a higher level of metabolism (induced in our rats by LAP treatment) increase choline requirements, the amount of choline chloride in our regular diet (100 mg. per 100 gm. of food) appears amply sufficient.

Summary. In the present paper the authors present a series of experiments, on the nephrosclerosis produced after anterior pituitary overdosage. The work deals particularly with the effect of diet (protein and B vitamin contents) upon the hypertension which accompanies this experimental condition. From the results the following conclusions were derived:

1. The LAP-nephrosclerosis was concomitant with a pronounced degree of hypertension in a high percentage of the animals, the hypertensive average being 157 ± 4 mm. Hg (standard error).

2. The hypertension produced by LAP treatment on a 30% protein ration was prevented by decreasing the casein concentration to 15%.

3. Five vitamins of the B group, namely, thiamine, riboflavin, pyridoxine, and calcium pantothenate, were inactive against the hypertension and nephrosclerosis but choline chloride had a slight beneficial effect if given in excessive amounts (1 gm. per 100 gm. food).

4. A very pronounced adrenal enlargement was always present in the hypertensive rats.

5. There was no statistically significant difference in adrenal weight between animals receiving a 15- or a 30%-casein diet. The difference was, however, highly significant if, in addition to the ration, the animals were simultaneously treated with large amounts of anterior pituitary.

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THE MANAGEMENT OF TETANUS WITH CURARE: REPORT OF TWO CASES

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Death from tetanus may result from spasm of the respiratory muscles, toxemia, pulmonary complications secondary to oversedation, or the cumulative effects of exhaustion, dehydration and inadequate nutrition. Tetanic contractions contribute importantly to the manifestations of the disease and, in the past, they have been treated usually by heavy sedation. The use of large amounts of sedatives is associated with a high incidence of pulmonary complications. Moreover, sedatives often fail to control adequately tetanic seizures. Curare, by blocking the transmission of the nerve impulse at the myoneural junction, reduces muscle spasm and results in marked muscular relaxation. Thus, it should be a valuable adjunct in the management of tetanic contractions. As long ago as 1894 Hoche[4] employed curare in the treatment of tetanus. More recently Cole,[1] Mitchell,[5] and West[6] have used either the crude drug or its chief active principle, curarine. However, in the past curare was not extensively employed in treating tetanus because the available preparations varied greatly in potency and the response to a given dose was unpredictable. In 1943 Cullen and Quion,[2] using a highly purified preparation of curare, satisfactorily controlled tetanic seizures in one patient. Pure preparations, standardized by biological assay, are now commercially available. The following case reports demonstrate the value of curare in the management of tetanus and illustrate a dangerous complication induced by it in one instance.

Case Reports. Case 1. A 40 year old laborer was admitted to Vanderbilt University Hospital, January 7, 1947, complaining of stiffness of the jaws and neck; 15 days previously he had crushed his right finger between two railroad ties. Tetanus antitoxin was refused because on several previous occasions nausea, chills and fever had followed its administration. The wound became infected locally without lymphangitis or constitutional symptoms. He felt well until 3 days before admission when he awoke with slight stiffness of the neck and jaws. There developed gradually increased muscular irritability. Sudden noises or jarring caused generalized painful muscular contractions. These symptoms steadily increased in severity. Eighteen hours before admission he became unable to urinate.

The past history was not remarkable except that in August, 1945, and on several previous occasions, he had received tetanus antitoxin following a minor injury.

Physical examination revealed a well-developed and nourished man who was in moderate discomfort. The neck was stiff and trismus prevented opening of the mouth more than 1 or 2 cm. There was generalized muscular hyperirritability. Slight jarring of the bed caused painful muscular spasms and dyspnea. The tip of the right ring finger was lacerated and pus was exuding from beneath the nail. The heart and lungs were normal. The abdomen was tense and the rectus muscles were spastic. All of the tendon reflexes were hyperactive.

The white blood cell count was 19,000/cu. mm. with 73% segmented forms.

Hospital course: Following a negative intradermal skin test for hypersensitiveness to horse serum, the patient was given 45,000

* Intocostrin is a curare preparation, standardized by biological assay, containing 20 units per cc.

units of tetanus antitoxin intramuscularly. Under sodium pentothal anesthesia the necrotic skin and the medial portion of the nail of the infected finger were cut away. *Clostridium tetani* was cultured from the débrided tissue. A filtrate of the culture of this organism produced convulsions in mice.

During the first 3 hospital days the patient remained moderately ill. The rectal temperature rose to 101.8° F. daily and there were frequent painful generalized muscular spasms accompanied by slight dyspnea. Catheterization of the bladder was necessary because of urinary retention.

The first injection of 60 units of intocostrin* was given on the morning of admission. It was followed immediately by marked subjective improvement and moderate muscular relaxation. Hyperirritability gradually returned and a second dose of 20 units was given after 1½ hours. A total of 9 intravenous injections of intocostrin,* ranging between 20 and 60 units each and averaging 40 units each, were given during the first 4 hospital days. Sodium phenobarbital was administered at frequent intervals and he received several injections of codeine for the painful muscular contractions. Penicillin in doses of 30,000 units at intervals of 3 hours was administered for 17 days. The doses of curare which were employed in this case were not sufficient to control the muscular contractions completely throughout each 24 hour period. Nevertheless, the results obtained indicated conclusively that curare caused muscular relaxation and alleviated the painful spasms and that it was more effective than codeine in controlling pain. The subjective relief provided by it was more impressive than were the objective signs of improvement.

The patient made an uneventful recovery and was discharged 19 days after admission to the hospital.

Case 2. A 38 year old caretaker was admitted to Vanderbilt University Hospital on February 23, 1947. On February 16 he noted stiffness of the neck and jaws, slight trismus and headache. He remained ambulatory until the day before admission when he experienced dysphagia, inability to open his mouth, generalized muscular stiffness and dyspnea. He had several painful tetanic seizures. There was no history of injury. He had never received tetanus toxoid or antitoxin.

The past history was non-contributory.

He was acutely ill and sweating profusely. Cyanosis was marked. The temperature was 100° and tachycardia was present. There was evidence of dehydration. There was marked opisthotonus, trismus, nuchal rigidity and generalized muscular rigidity. The characteristic sardonic facies was present. Speech was not impaired. The respirations were labored and stridulous although movement of the thoracic cage was almost imperceptible. The abdomen was board-like and the lumbar muscles were in a completely rigid state. The jaws could be opened only ½ cm. All of the deep reflexes were hyperactive. Over the knuckle of the right index finger there was a superficial abrasion 1 cm. in length which was covered by a dry crust.

The white cell count was 16,500, of which 86% were neutrophils. Lumbar puncture revealed normal cerebrospinal fluid. Cultures from the abrasion on the finger did not yield *Clostridium tetani*.

Hospital course: From the outset it was apparent that laryngeal spasm was severe and a factor in the production of the marked dyspnea and cyanosis. Within a 4 hour period, 140 units of intocostrin were given intravenously in divided doses. After sufficient intocostrin had been given to overcome the laryngeal and generalized muscle spasm, it became necessary to hold the tongue forward. Otherwise, it fell back in the mouth and occluded the glottis. However, respiratory paralysis did not occur. At intervals oxygen was administered by mask. Initially, the accumulation of secretions in the pharynx proved troublesome. Atropine appeared to be helpful in its suppression.

The patient exhibited negative skin reactions to horse serum and 40,000 units of tetanus antitoxin were administered intramuscularly. Penicillin in doses of 30,000 units intramuscularly every 3 hours was also given. Intocostrin was employed in doses of 40 units intramuscularly at 4 hour intervals with complete control of muscle spasms and trismus. Sodium phenobarbital 0.24 gm. daily, was administered. He was kept fairly comfortable on this therapeutic régime and was able to take food by mouth and to void and defecate normally.

The patient slowly recovered. He was given 10,000 units of tetanus antitoxin daily for 4 days, during which time the temperature remained slightly elevated. Penicillin

was discontinued on the 9th hospital day. Our supply of intocostrin became exhausted on the 9th day of treatment and for 16 hours none was administered. During this period nuchal rigidity and trismus reappeared and there were several mild muscular spasms. With the reinstitution of curare treatment these symptoms promptly subsided. Intocostrin was discontinued on the 18th hospital day. The patient was then able to sit beside the bed and in a day or so became ambulatory on the ward. He had completely recovered when discharged from the hospital 34 days after the onset of the illness.

Comment. The cases reported above demonstrate that curare is effective in controlling the most distressing manifestations of tetanus, *viz.*, painful muscular contractions. Whether or not treatment with this drug will lower the mortality rate in tetanus remains to be seen.

Curare acts at the myoneural junction by blocking the transmission of the nerve impulse. This action is due to the inability of the curarized muscle cell to respond to acetylcholine.[3] The release of acetylcholine by the neural impulse is not prevented by curare but the response to this chemical mediator is blocked. This blocking is not due to a paralytic action of curare because the involved cells are still capable of responding to electrical and other chemical stimuli.[3]

The principal dangers in the administration of curare are the development of paralysis of the muscles of respiration, paralysis of the tongue, and the accumulation of mucus in the air passages. In Case 2 muscular relaxation was so marked that the tongue dropped back and occluded the glottis. Mucus accumulated in the respiratory tract and was also a troublesome development.

Our experience with curare in these cases and the limited experience of others as recorded in the literature on the subject lead us to formulate the following statements regarding its use: The chief danger is weakness or paralysis of the muscles of respiration. Therefore, constant attention is mandatory. Neostigmine and physostigmine are physiological antagonists to curare and act immediately to relieve respiratory paralysis induced by it. One of these preparations should be kept by the bedside at all times while curare is being employed. Since these drugs increase bronchial secretions, atropine should be administered concomitantly. Artificial respiration may be life-saving when respiratory paralysis results from treatment with curare. It must be provided promptly and expertly until the curare antagonist, neostigmine, can be administered.

Summary. Two cases of tetanus treated with a curare preparation are reported. The efficacy of this drug in controlling tetanic seizures and painful muscular contractions is confirmed. The management of certain untoward reactions to curare when employed in the treatment of tetanus is discussed.

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CALCAREOUS AORTIC STENOSIS AND CORONARY ARTERY DISEASE*

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This study was undertaken to determine the degree of coronary sclerosis that occurs in patients suffering from calcareous aortic stenosis. Similarly the subjective symptoms of the patients were studied to determine to what degree they might be related to the existence and degree of coronary sclerosis.

Procedure. The material chosen for study consisted of the clinical histories and necropsy specimens in 100 cases of calcareous aortic stenosis selected with a view toward getting a representative number of cases in each age group. Stenosis of the aortic valve was graded according to the degree of occlusion of the aortic orifice. Less than 25% occlusion was designated as Grade 1; 25 to 49% as Grade 2; 50 to 74% as Grade 3 and 75% or more as Grade 4. The grading of the degree of sclerosis of the coronary arteries was done in the same manner as was also the grading of aortic sclerosis. In addition the hearts were studied in the gross for evidence of hypertrophy and for the presence of areas of old or recent myocardial infarction.

Table 1.—Frequency of Occurrence of Symptoms and Signs in 100 Cases of Calcareous Aortic Stenosis

	Cases
Dyspnea	69
Harsh basal systolic murmur	60
Enlarged heart*	53
Hypertension	29
Anginal type of pain	28
History of tonsillitis	27
Orthopnea	26
History of arthritis	25
History of rheumatic fever	19
Sudden death	18
Postprandial distress†	15
Dizziness	12
Jaundice†	4
History of chorea‡	2
History of syncope	1

* Compare the incidence of enlarged heart given here with that indicated by the mean heart weights in Table 3. In spite of clinical findings the heart is always found to be enlarged at necropsy even in the milder grades of stenosis.

† Not associated with any demonstrable lesion in the gastro-intestinal or biliary tracts.

‡ In neither of these cases was there a history of rheumatic fever.

Incidence of Symptoms and Signs in 100 Cases (Table 1). *Symptoms.* The most commonly occurring symptom in this series was dyspnea, which occurred in 69 of the 100 cases.

The next most common symptom was angina pectoris, which occurred in 28 cases. The term "angina" was applied only to those cases in which there was a definite history of retrosternal or substernal pain brought on by exertion and relieved by rest. In 10 of these cases mild grades (1 and 2) of aortic stenosis were exhibited while in 18 cases severe grades (3 and 4) of aortic stenosis were exhibited. Of these 28 cases, in 10 an additional complaint of postprandial abdominal distress in the form of mild pain, bloating and "indigestion" was made.

Also in 5 other cases in the series (not associated with angina) there was complaint of postprandial distress. In none of these 15 cases was any associated disease of the biliary or gastro-intestinal tracts demonstrable either clinically or at necropsy.

The symptom of orthopnea was encountered in 26 instances. Dizziness was noted 12 times and the complaint of syncope occurred in only 1 patient.

* Abridgment of part of a thesis submitted by Dr. Horan to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M.S. in Medicine

Signs. A harsh loud basal systolic murmur typical of calcareous aortic stenosis was heard in 60 patients, an atypical (usually an apical systolic) murmur was recorded in 19 cases and in the remaining 21 no murmur was recorded on the clinical histories.

Enlargement of the heart was noted clinically in 53 cases. Jaundice not associated with any clinical evidence of disease of the liver or biliary tract was noted in 4 cases and, in these, other signs of heart failure such as râles or edema were concomitant findings.

Electrocardiographic tracings were made in 52 of the cases (see Table 2). As would be expected the most constant findings were those suggestive of changes in the myocardium of the left ventricle as exhibited in the 15 cases in which frank left ventricular strain was evident and in the 12 cases in which merely left axis deviation was noted.[1,9]

TABLE 2.—THE ELECTROCARDIOGRAPHIC FINDINGS IN 52 CASES OF CALCAREOUS AORTIC STENOSIS*

	Stenosis, grade				
	1	2	3	4	Cases
Essentially normal tracing	1	1	1	2	5
Left axis deviation	3	4	4	1	12
Left ventricular strain	2	4	3	6	15
Left bundle-branch block	1	1	3	1	6
Auricular fibrillation	..	2	1	1	4
Auricular flutter	..	..	2	..	2
Right axis deviation	..	1	2	..	3†
Right ventricular strain	1	2	1	..	4†
Q_3 T_3 pattern	..	1	..	..	1

* In these cases inverted T_1 was encountered twenty-one times, inverted T_2 fifteen times and inverted T_3 twenty-one times.

† In these cases there were associated mitral lesions.

PATHOLOGIC CONDITIONS IN THE HEART AND BLOOD VESSELS FOUND IN ASSOCIATION WITH CALCAREOUS AORTIC STENOSIS. *Degree of Aortic Stenosis Contrasted With Degree of Coronary Sclerosis.* It is to be noted from Table 3 that in general, in accord with the findings of Dry and Willius,[8] there seemed to be a tendency for the degree of coronary sclerosis in this series to be inversely proportional to the degree of aortic stenosis. In 7 cases, obliteration of 25 to 75% of the lumina of the ostia of the coronary arteries was noted and of these 7, angina pectoris occurred in only 2 cases.

Incidence of Hypertension. Hypertension was noted in 29 cases. Of these, results of funduscopic examinations were recorded in 21 cases; 1 of these examinations gave negative results, 2 revealed senile changes and the remaining 18 disclosed typical hypertensive changes. In 3 cases in which hypertension was not detected by the sphygmomanometer, changes in the retinal arterioles characteristic of hypertension were found and in these 3 cases cardiac hypertrophy was noted at necropsy.

In 10 of the cases of hypertension in which characteristic retinal arteriolar changes were evident and in 4 of the cases in which results of funduscopic examination were not recorded, angina pectoris was present.

Associated Myocardial Infarction. Infarction of the myocardium either old or recent was found in 20 cases. In 7 of these the infarction was associated with both hypertension and angina pectoris, in 5 with angina pectoris alone and in 7 with hypertension alone. In the remaining case there was neither hypertension nor angina pectoris.

Cause of Death. Sudden death occurred in 18 cases. Of these, pulmonary emboli were found in 6 cases and 1 patient died apparently as the result of a reaction to plasma transfusion. The remaining 11 patients died either as a result of acute coronary insufficiency or death was in some way associated with calcareous aortic

TABLE 3.—COMPARISON OF GRADE OF AORTIC STENOSIS WITH GRADE OF AORTIC SCLEROSIS, MEAN WEIGHT OF HEARTS, MEAN DEGREE OF CORONARY SCLEROSIS AND INCIDENCE OF OSTIAL NARROWING BY AGE GROUPS IN 100 CASES OF AORTIC STENOSIS

Age (years)	Cases	Aortic stenosis (grade)	Aortic sclerosis (mean degree*)	Hearts (mean gm. wt.)	Coronary sclerosis (mean degree†)	Ostial narrowing (cases)
Under 40	3	3	1	626	1	1
40–49	3	1	2	425	2	
	1	2	2	685	1	
	5	3	1	627	1	
	3	4	2	795	1	1
50–59	3	1	3	427	3	
	10	2	2	494	2	
	7	3	2	655	2	
	4	4	2	596	1	
60–69	7	1	2	455	2	1
	3	2	3	385	2	
	5	3	2	483	1	
	4	4	2	717	2	1
70–79	13	1	3	387	2	1
	6	2	3	476	3	1
	8	3	3	637	2	
	4	4	3	556	2	
80–89	6	1	3	418	3	
	2	2	3	565	3	1
	3	3	3	447	2	
	0	4				

* The degree of arteriosclerosis of the aorta in this series seemed to be dependent on age rather than to bear any direct or inverse relation to the degree of stenosis of the aortic valve.

† All the coronary arteries exhibited some degree of sclerosis.

stenosis.[2,12,13] The primary cause of death in 42 cases was some pathologic condition of the heart; 58 patients died of other causes.

Comment. Calcareous aortic stenosis is a disease of the aortic valve which usually becomes manifest in later life. Stenosis of higher grades is almost invariably characterized by a harsh systolic murmur over the aortic area together with a coarse systolic thrill palpable anteriorly in the second and third right intercostal spaces; the diagnosis is further substantiated by the absence of the second aortic sound although this latter finding is not necessary for the diagnosis. In the lower grades or milder forms of stenosis the diagnosis may be made by demonstrating calcification of the aortic leaflets or the aortic ring on roentgenoscopic examination. The other diagnostic criteria are well known and need no further discussion.[15]

Although in this series a positive history of rheumatic fever was elicited in only 19 cases and a positive history of chorea was elicited in 2 additional cases, nevertheless the weight of evidence supports the view that calcareous aortic stenosis is a consequence of rheumatic fever.[3–8]

The work of others has shown that the lesion in question is usually found in persons in the older age groups.[8,10,11] Confirmation of this was not possible in the present series since the cases were selected with a view toward getting a representative number of cases in all age groups. However, in selecting these cases for study the impression was gained that in the great majority of all cases of calcareous aortic stenosis the lesion is first discovered when the patient is from 60 to 80 years old.

The relative mildness of calcareous aortic stenosis when compared with mitral stenosis is attested to by (1) the length of time between the actual attack of rheumatic fever and the clinical recognition of the valvular lesion and (2) by the frequency of occurrence of death from noncardiac causes (more than 50%).

The anginal type of pain which occurred in 28 cases was fairly uniformly distributed not only with reference to the various grades of stenosis but also with reference to the various age groups. The degree of coronary sclerosis on the other hand seemed to be, in a measure, inversely proportional to the degree of aortic stenosis. In all age groups there was more or less tendency for the higher grades of aortic stenosis to accompany the lower grades of coronary sclerosis and for the lower grades of stenosis to accompany the higher grades of coronary sclerosis. No conclusion as to a cause and effect relationship between aortic stenosis and angina pectoris can be drawn from this, however, since it is known that even in the absence of an aortic lesion, necropsy studies in a case in which the patient exhibited a severe anginal syndrome during life may, in rare instances, reveal only minimal coronary sclerosis. Conversely patients who never complained of angina may have coronary sclerosis, Grade 4, which is observed at necropsy.

Hypertension may occur in calcareous aortic stenosis with the same frequency as it does in other organic heart diseases. In this series the incidence of hypertension was 29%; 8 of these patients had Grade 1 stenosis of the aortic valve; 9, Grade 2; 8, Grade 3; and 4, Grade 4. From funduscopic studies in this series there is no reason to believe that the hypertension associated with calcareous aortic stenosis differs in any way from ordinary essential hypertension since 18 of the 21 pairs of fundi which were studied showed changes typical of essential hypertension. No retinal vessels in the series exceeded a Grade 2 narrowing or a Grade 2 sclerosis. White and Jones[14] in 1928, in a study of 3000 patients with cardiac symptoms, 2421 of whom had organic heart disease, found the incidence of hypertension to be 29.2% among those with organic disease.

The fact that 10 cases of angina pectoris occurred in association with the less severe grades of coronary sclerosis (but more severe grades of aortic stenosis) and that 18 cases of angina occurred in association with the more severe grades of coronary sclerosis (but less severe grades of aortic stenosis) suggests that the degree of coronary sclerosis does not explain all the mechanisms operating in the anginal syndrome. Other factors to be taken into consideration are: (1) the complete clinical picture which includes such points as age, pain threshold of the patient, presence or absence of an associated disease such as diabetes, hypertension, and so forth, and the presence or absence of a valvular cardiac lesion particularly of the aortic valve; and (2) the complete pathologic picture, which not only includes a study of the coronary arteries and their ostia but also the degree of scarring and hypertrophy of the myocardium and the degree of dilatation of the cardiac chambers.

Summary. A study of 100 cases of calcareous aortic stenosis is presented with particular reference to the degree of coronary sclerosis and the incidence of clinical symptoms and signs.

Some degree of coronary sclerosis was present in every case and this degree was found to be, in a measure, inversely proportional to the degree of aortic stenosis.

The most common clinical symptom was found to be dyspnea which occurred in 69% of the cases.

Of the patients 29% exhibited hypertension and 28% complained of anginal type of pain.

Infarction of the myocardium was exhibited in 20% of the cases.

Sudden death occurred in 18% of the cases.

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A STATISTICAL STUDY OF THE HEMATOLOGIC VARIABLES IN SUBJECTS WITH THALASSEMIA MINOR*

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Thalassemia[11] (Cooley's anemia, Mediterranean anemia) is an inherited hematologic disorder which, as its name implies, is limited almost entirely to racial groups originally living around the Mediterranean Sea. In the United States it is not infrequently seen in immigrants of Mediterranean stock and in their descendants. The disease exists in 2 forms: the severe, progressive, and almost invariably fatal form originally described by Cooley and Lee,[1] and the genetically related but milder form which has been the subject of numerous reports in the medical literature of recent years.[2,3,7,8,9,10,12,13] It has been suggested that the term "thalassemia major" be applied to the former and the term "thalassemia minor" to the latter.[10] This is in keeping with the close genetic and hematologic relationship of the 2 conditions,[3,6,10] and indicates that while they are qualitatively essentially similar, quantitative differences in severity exist. Thalassemia major occurs about one in each 2400 births to persons of southern Italian or Sicilian stock in Rochester, New York, while thalassemia minor occurs about once in 25 such births.[5]

The more qualitative hematologic characteristics of thalassemia minor are becoming well recognized. It is a condition distinguished by the occurrence in well-nourished persons of hypochromic, microcytic erythrocytes, not infrequently oval in shape or appearing as "targets" on the stained blood smear. Basophilic stippling is common. The hemoglobin values and volume of packed erythrocytes are usually but not invariably below the normal range. By comparison the total number of erythrocytes is disproportionately high. The erythrocytes characteristically show increased resistance to hemolysis by hypotonic saline. There may or may not be leukocytosis, reticulocytosis and elevated icterus index, or splenomegaly. In Italian subjects with thalassemia minor studied in Rochester, New York, leukocytosis and elevated icterus indices have been unusual and reticulocytosis of only slight degree.

The present report represents a statistical analysis of the hematologic findings in 82 subjects with thalassemia minor and is prompted by the apparent desirability of further clarification of the more quantitative aspects of this not uncommon disorder of the Mediterranean peoples. The data on which the paper is based have been compiled almost entirely from Italian subjects residing in Rochester, New York, or its environs and have been presented in part in previous publications.[6,10] In most instances these subjects were from southern Italian or Sicilian stock. In order to evaluate more adequately the hematologic defect, there are included similar studies on normal members of family groups in which thalassemia occurs. These normal individuals presumably share the same hereditary and environmental background as the subjects with thalassemia minor and are therefore especially suitable for comparison.

Methods. The hematologic studies were in every case made by one or the other of

* The major portion of the observations on which this paper is based were made while the authors were associated in the Department of Medicine of the University of Rochester School of Medicine and Dentistry and the Medical Clinics of the Strong Memorial Hospital and the Rochester Municipal Hospital, Rochester, New York.

the authors. All blood samples were obtained with careful attention to avoiding stasis or hemolysis and were placed in bottles containing both potassium and ammonium oxalate in the proportions suggested by Heller and Paul.[4] In blood so collected there is no alteration in the volume of the erythrocytes. In almost all instances erythrocyte counts were done in duplicate and averaged. Only Bureau of Standards certified equipment was used. Hemoglobin determinations were made according to the method of Sahli employing carefully calibrated hemoglobinometers. The volume of packed erythrocytes was determined by centrifuging a properly filled Wintrobe hematocrit tube at 3000 r.p.m. for 1 hour. No subject in which there was any question of the diagnosis was included in the analysis. Similarly no subjects were included in which known coexistent disease might distort the blood findings. In the majority of instances family group studies were made.

PRESENTATION OF DATA. The data are best presented in tabular and graphic form. Table 1 indicates the means and standard deviations of the hematologic variables subjected to analysis. The data is broken down into different age groups since well-recognized physiologic variations from normal adult values are found in children of different ages. In the adult groups females and males are analyzed separately. In all groups 14 years of age or younger females and males are grouped together. The numbers included in certain age groups are so small as to render statistical constants of little significance.

TABLE 1.—MEANS AND STANDARD DEVIATIONS OF HEMATOLOGIC VARIABLES FOR NORMAL AND THALASSEMIC SUBJECTS FROM THE SAME ITALIAN FAMILY GROUPS

			Hemoglobin (gm. %)		R.B.C. (millions per c.mm.)		Volume of packed R.B.C. (%)		M.C.V. (cμ)		M.C.H. (mμ)		M.C.H.C. (%)		% saline at which complete hemolysis occurs	
Aged	Group	N	Mean	σ	Mean	σ	Mean	σ	Mean	σ	Mean	σ	Mean	σ	Mean	σ
1- 4	Normal	5	13.1		4.56		37.9		83.5		29.1		34.5		0.30*	
	Thalassemic	9	11.4		5.72		36.4		63.8		19.9		32.4		0.21	
5- 9	Normal	3	13.6		4.72		39.9		84.8		29.1		34.1		0.30	
	Thalassemic	6	11.7		5.88		37.4		64.0		20.0		31.3		0.23	
10-14	Normal	4	14.2		4.70		40.9*		84.2*		30.4		35.7*		0.31*	
	Thalassemic	9	12.0		5.95		37.3		63.8		20.6		32.3		0.22	
Adult males	Normal	21	16.2	± 1.27	5.27	± 0.550	45.8	± 2.42	87.6	± 6.13	30.9	± 2.35	35.3	± 1.89	0.31	±0.022
	Thalassemic	27	13.5	± 1.35	6.12	± 0.620	42.1	± 3.50	69.0	± 4.97	22.0	± 1.73	32.0	± 1.59	0.23*	±0.027*
Adult females	Normal	21	14.1	± 0.90	4.67	± 0.414	40.6	± 2.19	87.4	± 5.81	30.4	± 2.29	34.7	± 1.37	0.31	±0.014
	Thalassemic	31	11.8	± 1.15	5.59	± 0.430	37.3	± 2.88	67.0	± 6.02	21.2	± 2.29	31.7	± 2.00	0.23	±0.029

All age groups with the exception of adults include both males and females.
N, number of subjects. σ, standard deviation.
* Based on 1 less than N.

Figure 1 indicates graphically the populations of hemoglobin values for individuals with thalassemia minor as compared with individuals from the same family and racial groups not having thalassemia minor. In both the normal and thalassemic groups females are designated by a different symbol than males.

Figure 2 shows the % of individuals above 15 years of age having hemoglobin values within the arbitrarily designated ranges. The control figures given were as in Table 1, derived from the non-thalassemic members of the same family groups

Figure 3 indicates the % of individuals having erythrocyte counts within arbitrarily designated ranges. The data are analyzed for the same individuals and in the same manner as in Figure 2.

Discussion. The present analysis serves to underline and to quantitate some of the already recognized features of thalassemia minor. It can readily be seen from the table and figures that individuals with this condition have a definite and significant hematologic defect in comparison with normal members of the same family groups, and this difference is already well established in childhood. On the average in adults of both sexes this defect amounts

to a deficiency of 2 to 3 gm. of hemoglobin per 100 cc. of blood. It is also readily apparent that this defect is superimposed on the normal patterns of male and female blood pictures. Thus males with thalassemia minor showed substantially higher hemoglobin values than did females similarily affected. This difference was of the same order of magnitude as differences observed between normal males and females in the same study.

The marked tendency for all individuals with thalassemia minor to have an elevated erythrocyte count is strikingly shown in Table 1 and Figure 3. The mean values for erythrocyte counts in both females and males are well above those found in normal individuals even in the face of the substantially low hemoglobin values. This tendency to "polycythemia" has been commented upon before but in Rochester Italians it is almost uniformly a characteristic part of the pattern. Thus, including both males and females only 2 out of 58 adults with thalassemia minor has erythrocyte counts below 5,000,000 per c.mm. In 48.3% of thalassemic females and 85.8% of thalassemic males the counts were above 5,500,000 per c.mm. The tendency to "polycythemia" was, as might be expected, more prominent in males, 57% of whom had red cell values in excess of 6,000,000 per c.mm.

The mean corpuscular volumes and mean corpuscular hemoglobins are, of course, markedly below normal. The mean corpuscular hemoglobin concentration is, on the other hand, not nearly so markedly lowered as are the first 2 constants. This means that while the individual cells are of markedly low volume and hemoglobin content, each cell *for its volume* is only moderately deficient in hemoglobin. Stated otherwise, each unit of cell contains only moderately less hemoglobin than each unit of a normal erythrocyte, but the cells themselves are small in volume.

It must be remembered that the data presented are based on studies made from relatively homogeneous racial stock in a single American city. The individuals studied are almost uniformly of southern Italian or Sicilian extraction. It may be that racial factors alter the characteristic pattern in other Mediterranean peoples. The data probably represent a suitable cross-section of the usual hematologic findings in the racial groups studied.

The biologic significance of the degree of hematologic defect exhibited by indi-

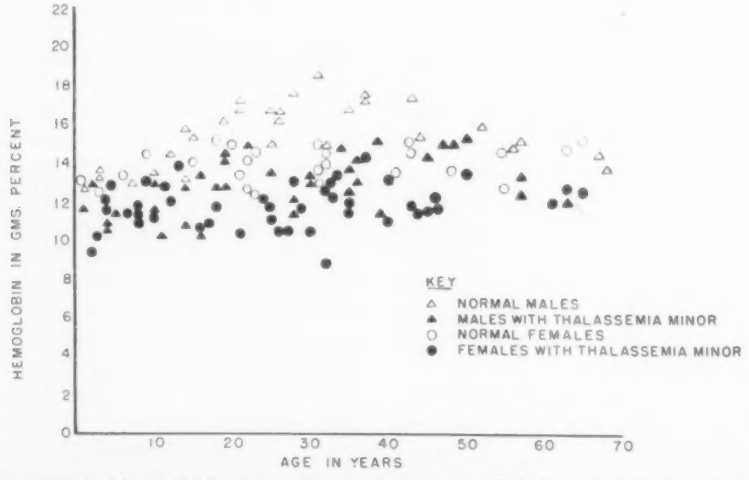

FIG. 1.—Individual hemoglobin values observed in normal and thalassemic members of the same family groups.

viduals with thalassemia minor has been discussed in a previous report.[6] It is difficult to assess but most probably these individuals have approximately the same handicap as an individual with iron deficiency of comparable severity. Just what the defect means in terms of meeting such increased hematopoietic demands as pregnancy, blood loss, and infection is not now known.

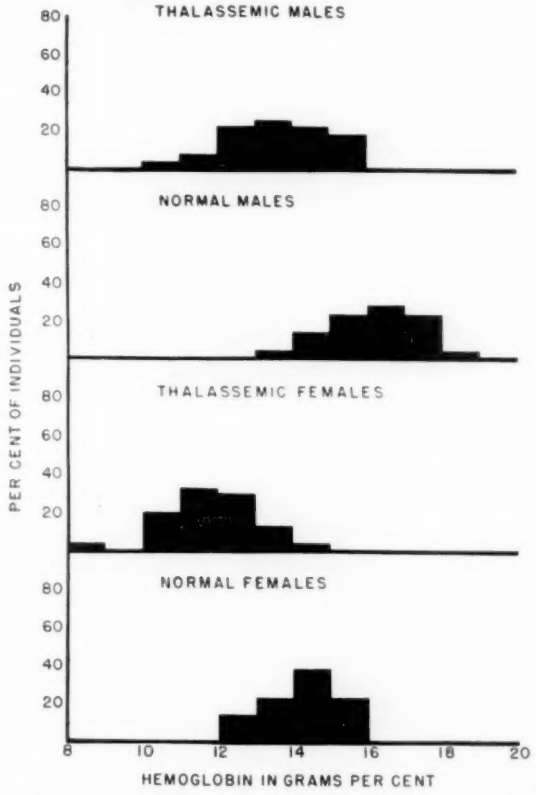

FIG. 2.—Per cent of normal and thalassemic individuals from the same family groups having hemoglobin values within various designated ranges. Only individuals 15 or more years of age are included

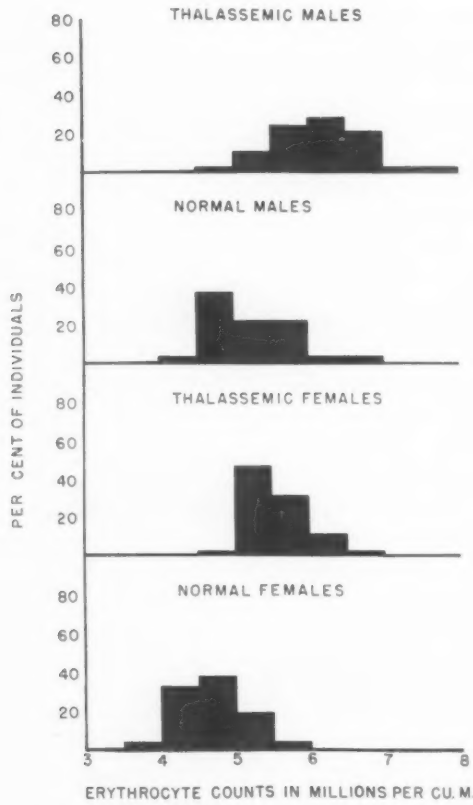

FIG. 3.—Per cent of normal and thalassemic individuals from the same family groups having erythrocyte counts within various designated ranges. Only individuals 15 or more years of age are included.

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PROGRESS
OF
MEDICAL SCIENCE

DERMATOLOGY AND SYPHILOLOGY

UNDER THE CHARGE OF

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SOME PROBLEMS IN THE BIOLOGY OF THE SYPHILITIC INFECTION

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GREAT advances in the therapeusis of a disease have an unfortunate tendency to discourage fundamental research, and to create an impression even among critical minds, that the disease in question being now "in the bag" there is no further occasion for hunting. In the case of syphilis, and indeed of all the venereal group of infections, such a reaction is particularly unfortunate; for these diseases carry in their own biology and clinical course the means of their indefinite perpetuation. The inconspicuous onsets, and prolonged period of infectivity in which little incentive to diagnosis and treatment exists, as well as the margin of non-cure (still existent in syphilis at least) assures the transmission of the infection to fresh individuals, and the maintenance of a reservoir. Before the venereal diseases are conquered an immunizing procedure must be developed, a vaccination of high if not absolute effectiveness, to protect the originally uninfected person through long periods if not through life; and to prevent reinfection, which is now suspected of being a loophole through which magnificent cure possibilities leak away to relatively unsatisfactory epidemiologic results.

The field of needed research is a large and inviting one, to which, for example, 2 recent reviews by Beerman[1a,b] have directed attention. The clinical mechanisms underlying the symptomatology of syphilis are so far from understood as to justify the maintenance for years of clinical centers for the study of such problems as the nature of latency, the meaning of serologic tests in relation to the biology of the disease and its cure, the non-specific mechanisms of bodily reaction (serologic false positives) and of defense against infection. The calm assumption that reagin is a substance; that antisyphilitic drugs exert their entire effect directly upon the organism of the disease without the intervention of intermediate agencies provided by organ and tissue function in the host, and by cellular and biochemical (even enzymatic) agents indispensable to therapeutic effect, are familiar examples of syphilologic naivete. The only intermediates thus far given even a hearing

have been Lævaditi's bismoxyl, glutathione and most recently the "spreading factor," hyaluronic acid. The basis of crippling symptoms such as the lightning pain and the gastric crisis of tabes, both often at their worst after the serologic signs of activity of the disease have been reduced to negative is wholly unknown. More than 40 known conditions give rise to a serologic reaction in the blood similar to that of syphilis; almost nothing is known about the false positive in the spinal fluid. All the therapeutic agents used in syphilis, including mercury, bismuth, iodide, the arsenicals, penicillin and fever are effective against conditions as widely different from syphilis as lichen planus and subacute bacterial endocarditis. Disease due to fungi, to a wide range of bacteria, to protozoa, and to the allergic state, responds and under some circumstances fails to respond to treatment for syphilis in as yet unexplained fashion. Many of the clinical problems presented by syphilis particularly in the field of infection allergy are capable in their study and solution, of throwing much light on human diatheses which are still obscure. Even the influence of climate has its important syphilologic aspects, side by side with diet and endocrine balance and function. Such statements only touch the surface of the possibilities.

It is evident then that to the investigator with intestinal fortitude and ingenuity, there is no excuse for retiring from the clinical or the experimental field offered by syphilis. The purpose of this review, to some extent supplementary to Beerman's[1a,b] is to indicate directions, particularly in the study of the causative organism, in which the demand for more work is imperative.

Before opening the discussion, it is well to call attention to 2 basic investigational warping factors that are sometimes underestimated. They crop up in the proceedings of meetings more often than in the actual literature. These are-the interpretation of *in vivo* as compared with *in vitro* results, and the transfer of inferences based on animals, directly to the behavior of man. Bottled and test-tubed spirochetes are by virtue of their lack of virulence, an artificial product, whose very identity is often controversial (discussion of the Reiter strain, for example). The asymptomatic infection of the rat and the symptomatic disparities between the course of syphilis in the rabbit and in man particularly with reference to the more serious late manifestations are illustrations of vital differences in behavior and host parasite relationships that affect final conclusions on the applicability of experimental results to man.

Cultivation of Virulent Treponema Pallidum. It is generally conceded that this ultimate and fundamental desideratum has not been achieved. The problem of cultivation alone, whether of virulent (animal to medium) organisms or of long-standing avirulent strains is highly complex and involves control factors easily overlooked. Frazier mentions the maintenance of anaërobiosis as becoming increasingly difficult as the use of turbidimetric methods of estimating growth are applied (*e. g.*, agar cannot be used as the basic medium). Whiteley and Frazier[45] used sodium thioglycolate as the agent of choice. These investigators rate albumin as the common essential ingredient of the fluid constituents of spirochetal culture media. From this point, working with the Reiter strain, they have succeeded in producing a clear medium with only known chemical ingredients which satisfies the nitrogen, carbohydrate and vitamin requirements for the growth and subculture of the Reiter strain of *T. pallidum*. From such a stable controllable base as this, the problem of what constitutes or fosters growth and perhaps virulence in a culture medium can presumably be attacked.

Approaching the problem from a different direction, are the attempts to grow virulent *T. pallidum* in the chick embryo as described by Sterzi and Staudacher,[37] Callaway and Sharp,[6] Wile and Snow[53] and Wile and Johnson.[50a] None of this

work has progressed farther than to show that *T. pallidum* can be kept alive and virulent in the chick embryo for periods ranging from 2 hours to 8 days (1 experiment in 5). Evidently the conditions are in the main adverse under present techniques, and the fact of growth has not been demonstrated. Steinhaus and Hughes[36] have found an unknown spirochete in hen tissue and chick embryos as a complicating interpretative factor. The preservation of virulence under freezing conditions has been demonstrated by Turner[42c] up to 1 year in solid CO_2 and alcohol at $-78°$ C., and has its application in the use by Magnuson *et al.*[21] in attempted immunization by lyophilized organisms (see below). Probey[32] has recently reviewed the existing literature on the viability and virulence problem in lyophilized serum and has shown that *T. pallidum* becomes avirulent during the deep-freezing and drying process. Bessemans[2b,c] and Kast and Kolmer[13] have called attention to morphologic change in *T. pallidum* as it adapts itself to life in culture as against life *in vivo*, the thicker forms and flatter curves being associated with culture and the thinner more mobile forms with the struggle for existence in tissue.

Speaking with the presumption of clinicians on offering suggestions on laboratory problems, it would seem to us that the problem of virulence will be advanced toward solution by (1) a study of morphologic differences between virulent and avirulent living spirochetes to which the electron microscope lends itself; (2) development of a technique of mass cultivation of avirulent spirochetes such as has so substantially advanced the study of the chemistry of the tubercle bacillus and the pneumococcus; (3) mass isolation of large numbers of virulent *T. pallidum* from giant syphilomas (granuloma tissue chancres) in rabbits for chemical studies; (4) study of the effect of changes in the chemical and physical constitution of media on morphology, longevity, motility and ultimately virulence of both virulent and avirulent spirochetes; (5) and passage of *T. pallidum* through specific tissues to modify its virulence and to develop tropisms; this to include utilization of tissue culture and tissue extracts, and even hormones for such purposes.

THE SYPHILITIC ULTRAVIRUS PROBLEM. The existence of some form of ultramicroscopic agent in the pathologic mechanisms of syphilis has long seemed a theoretical necessity. Conspicuous among the phenomena to be explained are the apparent absence of spirochetes in infective lymph node material, the paucity of spiral organisms in the tissues of latent infections, and in late syphilitic granulomas, whose infectivity could only be demonstrated by animal inoculation. The attempts to prove an explanation have involved the assumption of a life cycle for the organism, with a difficultly demonstrable granular or resting stage; and the positing of an ultramicroscopic, filter-passing transmutation form of virus, alternative to the spirochetal form so long familiar in dark-field and tissue preparations. Pre-World War II investigators busied themselves mainly with observations and theorization regarding a life cycle (Warthin and Olsen,[46a,b] Ingraham[11] and Stokes.[39]) The post-war studies have shown a swing toward the virus type of hypothesis, under the impetus furnished by the electron microscope, by the studies of mouse-brain filter-passing inocula and indirectly by demonstrations or announcements in other fields of the transmutation of other bacteria (*Eberthella typhosa*, streptococci and of *Leptospira icteroides*) from a visible to an ultramicroscopic form. It would seem specially important that such announcements as those of Kendall[14] and of Rosenow and Oftedol[34a,b] on virus or ultravisible transmutations by alteration of growth media be put to the test on existing strains of spirochetes as soon as such studies as those of Whiteley and Frazier[48] have led to a synthesizable and controllable growth medium. Meanwhile the electron microscope has demonstrated intraspirillar granules and confirmed the

existence of the spore-like bud or knob described by investigators on microscopic evidence. It may well be hoped that the mode of reproduction of spirochetes will now be clarified, including the long-desired proof of growth of a spirochete from a Meirowsky[26a,b,c,d] or argentophile or spirochetogenic granule. Whether the intrafilamentous granules demonstrated by the electron microscope in the photographs of Mudd *et al.*,[28,29] Morton and Anderson,[27] Wile and Kearney,[51] Wile, Picard and Kearney[52] are degeneration products of a virus transmutation may perhaps also be determined (*Cf.* Levaditi[16b]). Bessemans *et al.*,[3] long a vigorous opponent of the ultramicroscopic phase concept, has attacked the problem with a micromanipulator with as yet inconclusive results. Levaditi[16a,17] considers the evidence of the existence of an ultrafilterable virus inadequate, on the basis of experiments in the infectiousness of the suspensions passed through collodion membranes of various meshes. He concludes that the syphilitic infectious agent will not pass meshes which should pass true ultraviruses. In a comparative study of several species of spirochetes, Séguin[35] believes he has proved that the conversion of a filter-passing spirochetogenic granule into a spirochetal filament is a common transformation among spirochetal organisms.

Johnson and Wile's[12] observations on the infectivity of filtered mouse-brain suspension in "carrier" mice are of particular interest as defining some of the conditions under which transmission in the absence of visible spirochetes and under various grades of filtration may take place. Johnson and Wile's experiments showed that mouse-brain added to infective suspensions of syphilitic rabbit testicle inhibits their infectiousness, and that infectiousness of mouse-brain tissue itself is lost by passage through a coarse Mandler filter.

These 2 investigators had previously proved that mouse material capable of transmitting the disease contained neither spirochetes nor histologic changes characteristic of syphilis. Wile's[49] most recent study indicates that the non-visible agent can be carried through as many as 4 passages from mouse to mouse without becoming visually demonstrable and that the pooled suspension of mouse liver, spleen and gonads in which it is present retains its virulence longer than does the brain emulsion.

In the summary of the invasion mechanism given below, mention will be made of studies in the minimum inoculum of spirochetes that will transmit the disease, which offer an explanation based in the infection potentiality of small numbers of spiral organisms, the alternative conception of an ultravisible form, to account for transmission by apparently spirochete-free suspensions.

The search for spirochetal forms and derivatives, and a possible ultravirus in tissue is making slow headway. Stroesco and Vaisman,[38] in Levaditi's laboratory, have developed a silver impregnation method applicable to frozen section only, by which it was shown that spirochetes are demonstrable thus far only in infected mice of the first generation, and are few in number. They are not present in second and later inoculations. Lépine told Wile in a personal interview that these spirochetal forms were in his opinion non-virulent and that he believed, from a large experience, the infection was carried from mouse to rabbit by an infravisible or granular stage of the organism. The development of freezing microtome methods producing exceedingly thin sections and frozen dried preparations (Wycoff[54a,b]), and using satisfactory high-speed microtomes already commercially available, should make possible the liberation of the search for spirochetal life cycle forms and for the ultravirus in tissue from some of the artefacts or alleged artefacts in fixed and stained tissue confusable with them. The boldest expression to date on the matter of ultravirus in tissue from late syphilids was a recent statement of Rakhmanov and Mashkilleison[33] before a local Philadelphia

meeting—that of the Philadelphia Chapter of the American-Soviet Medical Society on Sept. 24, 1945, which, however, in the *American Review of Soviet Medicine*, was toned down to an "under investigation" level. The best summary currently available of *T. pallidum* life cycle or other variants in tissue is that of Olsen,[30] one of Warthin's pupils and co-workers.

THE INVASION MECHANISM. *Via* the grapevine and cloakroom discussion at meetings, it is becoming clear that the transmission of syphilis, not to mention gonorrhea, to man by inoculation even by the "normal" mechanism of sexual exposure to infected contacts is not a simple or unvaryingly successful affair. It has long been suspected that the rise and fall in the incidence of syphilis in populations and countries is conditioned by other factors than the mere prevalence of infective exposure; but apart from some guesses as to the rôle of immunity conveyed by the peak of the preceding "epidemic" wave, in producing a fall of incidence, no conception of the mechanism of resistance to infection has arisen. It is to be hoped that the details of experience in the Guatemala project under Mahoney's[23] direction will not be withheld from publication by diplomatic or other considerations.

Pending further information on factors governing resistance to invasion, the increasingly clear demonstration and accurate timing of the spread of spirochetes from their inoculation site should be noted. The data reviewed by Turner[42d] and the observations of Levaditi, Vaisman and Rousset-Chabaud[18] which are couched in terms of days, are merely confirmatory of the painstaking work of earlier investigators including Brown and Pearce.[5] Kolle and Evers[15] brought the time of dissemination from inoculation site to regional lymph node down to minutes, the average of several investigators' results ranging around 35 minutes (Bessemans,[4] Levaditi[19] and others). Mahoney and Bryant[24] showed that actual invasion of the intact mucosa of the preputial sac of the rabbit required 3 to 4 hours, but they were obliged to use cotton packs impregnated with the spirochetal emulsion, a situation hardly comparable to "physiologic" inoculation. It may be be seen that in all this experimental work, now a decade or more old, little has been accomplished toward the delineation of the conditions in man under which infection does or does not follow exposure. Frankl[9] as well as Charpy[7] showed that the *T. pallidum* can be present in the normal skin of syphilitics without providing any of the histologically recognizable stimulus to lesion formation.

That the size of inocula, that is, the number of treponemes by actual count, influences invasion and infections as far as symptomatic character is concerned, has been one of the interesting developments of the decade. The studies all suffer from a common element of uncertainty in that they accept the spiral organism as the infectious element and give no consideration to the possibility of an accompanying ultramicroscopic invader (see summary above on mouse-brain inoculation). In 1943, Thomas and Morgan[41] carried out pioneer experiments on isolation and attempted inoculation of single *T. pallidum* obtained under dark-field with the Chambers micromanipulator. They failed to secure infection with doses of 1 to 6 organisms. They concluded, however, that a negative tissue transfer does not preclude the presence of *T. pallidum* in the inoculum or the absence of syphilis in the source animal. As a condition on the use of lymph node transfer, as a test of infection one must now recall the reported statement of Bessemans made in discussion of Moore before the Microbiological Congress, in Copenhagen (1947), on criteria of penicillin cure, that a transfer may be negative at 6 months but positive after 2 years.

The whole subject of inoculation on mechanism has been materially advanced by the presentation at the April 1947 symposium on Recent Advances in the Investigation of Venereal Diseases, Wash-

ington, D. C., of the observations of Magnuson, Eagle and Fleischman[20] on the minimal infectious inoculum of the Nichols strain of *T. pallidum*. This study reviews the literature, goes carefully into the mathematic estimation of the error of the methods employed by the authors and reaches the conclusion, contrary to Thomas and Morgan's, that 1 or 2 treponemes per inoculum are regularly infectious for 47% of rabbits intratesticularly inoculated. Two treponemes introduced through the *skin* are infectious for half the inoculated animals. A gradually ascending percentage gradient of successful inoculation was demonstrated as a function of increasing size of inoculum, up to 100% with 200,000 organisms. The *incubation period* of the animal infections was the same for inocula from 1 to 100 organisms (35 to 41 days) but fell sharply above that level to 27 days with 10,000 treponemes and 17 days with 200,000. The study indicates the importance of time factors in removal and inoculation, and the concentration of serum and tissue extractives in the inoculum.

Again, without minimizing the great importance of such tangible experimental results, it must not be forgotten that they deal with inoculation and invasion conditions probably quite different from those prevailing in the "natural" inoculation of man.

THE ASYMPTOMATIC INFECTION AND CARRIER PROBLEM. "Is a lesion and in particular a spirochete-rich lesion, essential as source to the human-to-human contact transmission of syphilis" phrases the eminently practical form that this problem takes in the epidemiology of the disease. "Can an asymptomatic individual transmit the disease?" and "What is an asymptomatic infection?" are 2 practical collaterals that must be constantly kept in mind. The late Dr. Warthin never tired of insisting that latency is a combination of undercover activity and of reactionless symbiosis, for which he used the "miliary gumma" or microreaction in the wall of the aorta (whose ability to produce animal inoculation syphilis has recently been demonstrated by Hu, Liu, Chen and Frazier[10]) and the hordes of treponemes in the apparently normal muscle of the heart of the congenital syphilitic, as respective illustrations.

Bessemans[2a] has provided one of the best summaries of the essentials of asymptomatic infection in the rabbit, still weighty after a decade, and quotable from the abstract in *Venereal Disease Information* as follows: "He finds that there are a number of factors involved, some of them in the parasites and some in the host. The number of cases of asymptomatic syphilis is increased by anything that limits the virulence of the parasites. Young strains, for instance, cause a higher percentage of asymptomatic cases than older ones, as if the progressive adaptation of the parasite to the host increased its virulence. The number of parasites used seems also to have an effect, though there seem to be exceptions to this rule, and there are cases in which asymptomatic syphilis is not produced by the lowest dilutions. Intratesticular inoculation generally causes a manifest syphilis, while inoculation into certain other tissues of the rabbit, such as the nervous system, the suprarenal capsule, the blood, the skin, and mucous membrane, the eye, and the kidney only causes symptomatic syphilis. There are certain individual differences in the animals. Adult female animals show a higher percentage of asymptomatic syphilis than young males. When the animals are in poor general condition, the percentage of asymptomatic cases is greater. A high temperature in the tissue tends to increase the number of asymptomatic cases. Dujardin claimed that the number of cases of asymptomatic syphilis is influenced by the allergic condition of the animals. The author tested this statement and did not find that allergic hypersensitiveness had any relation to the number of asymptomatic cases. However, he thinks that this question of an allergy

requires further study before a definite opinion can be pronounced."

Once it is possible to isolate with the micromanipulator individual treponemes in the symbiotic state from tissue (as in Frankl and Charpy's observations) and to test their virulence for animals, we shall have made a first step toward the basic interpretation of the carrier state and the question of tissue reaction in its relation to virulence. In this connection much of Besseman's statement should be kept in mind along with Johnson and Wile's[50b] observation on the virulence inhibiting qualities of mouse-brain tissue, etc.

Asymptomatic Infection and the Carrier State. A number of recognized facts have tended in the biology of the syphilitic infection, to dissociate infectivity and virulence of the organism from the mechanisms of microscopically visible tissue reaction in the form of lesion development and of lesion involution and healing. The identification of a carrier state in the rat has been followed by its demonstration in the white (albino house) mouse and other species of mice; and in several species of hamsters. These animals are then so far as visual evidence of syphilis is concerned merely test-tubes. The golden hamster[50b] does not even develop a positive seroprecipitation reaction (Kahn test) for the disease. Search of the organs and infective tissue material (Weller, quoted by Wile[47]) reveals neither demonstrable tissue changes of syphilitic type nor spirochetes by the Warthin-Starry silver impregnation. Yet the infection is transmissible to rabbits in practically all instances by such material. In the Jacobs and Heidelberger series of chemotherapeutic pentavalent arsenicals which led to tryparsamide, a compound was prepared which caused rapid healing of the lesions without destruction of spirochetes.[40] In fact, they flourished, and the animal infection generalized while the lesion vanished. Whole schools of thought such as the French pediatric group, led by Hudelo, have implied the clinical existence of man of asymptomatic mass infection with vague constitutional consequences to the third and fourth generation. The tie-in of the animal asymptomatic state with size of inoculum seems generally accepted (see above) and few enough organisms gaining entrance can lead to prolongation of incubation period and absence of demonstrable lesions. Pariser,[31] who has provided a full review of this literature, examined directly the transmissibility of syphilis by the genital mechanism in a study of the infectiousness of semen and of vaginal secretions in the human, in which he found that the semen of the male is not infectious unless a spirochete-containing lesion is present in the tract, and the vaginal secretions are not infectious unless there is an abnormal cervix (or by implication also a uterine lesion) or the woman is menstruating. How consistent over the life span of such an individual this non-infectiousness as a carrier may be requires much further study. What Pariser has shown thus far would seem to be that in the human subject asymptomatic infection does not exist, but only an asymptomatic state punctuated by symptomatic interludes. If there is any way other than by the development of lesions or by discharge through blood or physiologic secretions that the infective agent can be released from the asymptomatic body test-tube, it is as yet unknown. It might be studied with a little better chance at solution by maintaining uninfected and infected injured and uninjured individuals in contact and by interbreeding infected and uninfected animals such as the hamster.

The clinical evidence for a genuinely asymptomatic state in the human subject involves such problems as the unaccountable but persistent high-titer serologic test for syphilis. Such tests are now complicated by all that is known and not known about the specificity of serologic tests; and by the type case of an asymptomatic but faintly stigmatized or "suspect" victim of what may be a congenital infection as the only one in a large family

otherwise free from evidence of the disease.[40]

IMMUNIZATION AND IMMUNITY-SUSCEPTIBILITY PROBLEMS. The clinician and the public health officer, viewing ruefully the inverse relation between the spread of venereal disease and its increasingly ready response to an increasingly simplified treatment, realizes that in the direction of immunization lies the most important single hope for the extinction of syphilis. The difficulties of the problem can be imagined from the foregoing discussions of the biologic mechanism. It is therefore small wonder that so little systematic effort has been expended on the problem. One must first clarify innumerable problems, recently reviewed by Urbach and Beerman[45] in their discussion of immunity and allergy in syphilis. Not the least among them is the still unsolved problem of the manifestations induced in late syphilis by the injections of spirochetal suspension, purified or tissue-free, and suspended in tissue menstrua. One becomes entangled with a non-allergic phase of reaction, as in ordinary luetin tests and with homologous and pseudoreactions induced by such agents as potassium iodide, in late syphilis and congenital syphilis especially. There is needed, too, a much more precise understanding of the anergic or tissue non-reactive state in syphilis in its relation both to host and to spirochetal constitution.

Nonetheless, bold attempts to leap the fence of unknowns deserve vigorous commendation and support, in the hope that a new Jenner may arise among us. The work of Turner and his associates[8,25,42a,b,c,43,44] has included studies of yaws and the *T. pertenue* and *T. cuniculi* as well as *T. pallidum*. His most recent paper[44] reports the development of various degrees of cross-protection against infection by these 3 organisms in the rabbit. The recent papers of Magnuson and co-workers[21,22] deal with the rate of development of immunity to infection in the rabbit and currently[21] with an attempt at immunization of rabbits against killed *T. pallidum* and adjuvants (*M. phlei* emulsion in oil). The attempt at immunization was a failure, although the animals developed positive serologic tests for syphilis. The method of testing transmission was that of lymph node transfer, which is not free from objection.

The use of spirochetal vaccines for the treatment of syphilis including the Hilgermann preparation of supposedly *T. pallidum* has been reviewed by Urbach and Beerman with the statement that no significant conclusions have thus far been established. The conditions for which it has been used are all known to respond to treatment of low specificity like that of gumma to iodide.

The sketchiness of our knowledge of even this selected list of problems in the biology of syphilitic infection leaves an indelible impression of the need for further and still more ingenious research. Among the categories of unsolved problems one should list in addition to those above considered, the matter of strains and elective localization; the possible tropisms of the organism; the host side of tropism or tissue susceptibility and immunity which might be studied by tissue culture; the problems of infection allergy; and the defense mechanism of the host, including specific cell function within the tissue reaction against the infection (*e. g.*, the lymphocyte and the plasma cell), and the influence of the spreading factor on the course of a syphilitic infection. From some of the observations on the serologic responses of vaccines it is only a step to the study of the nature, and the question even of the existence, of specific reagin as a chemical entity. The exploration of the non-specific reactive mechanism of serologic tests is only in its beginnings. May it not be conceived that reagin will turn out to be not a substance but a ratio, and the serologic reactive mechanism of the body a type form or habit of reaction induced by a variety of agents, chiefly infectious in origin?

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OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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FACIAL RESTORATIONS IN MEDICAL PRACTICE

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A PROSTHESIS (*πρόσθεσις*), a putting to, from *προστιθημι*, to put to) is an artificial substitute for any missing part of the body. Since most such corrections are for facial deformities and defects, much of the literature and the interest is concerned with facial restoration.

As described by Brown,[1] prostheses should be looked on as of 2 types: 1. The type indicated when surgical intervention is contraindicated. Here are included cases in which coëxisting disease or other disability makes surgical treatment inadvisable and cases in which surgical manipulation of the tissue would end with esthetically undesirable results.

2. The second type of prostheses (which Esser has called the "bloody" type) are those which necessitate surgical incisions for their establishment. The sculpturally molded synthetic implants come under this heading. What is the difference between the synthetic materials here described and the previously used ivory, celluloid and cartilage? These materials are molded from sculptured models; they do not slip out of place, since they fit only 1 area; they do not curl and will not shrink, nor have they been found to be a source of irritation of tissue because of composition.

The appearance of new literature to describe artificial substances and the technique of building these materials as substitutes for missing parts of the body indicates the limitations of materials that plastic surgeons have had to work with. Problems of the shape of the cartilage and the bone of the donor, of the absorption of the transplanted living material and of hand molding of cancellous bone have limited the sculptural effects otherwise possible in plastic surgery.

But really clever implantation techniques have been devised by imaginative surgeons. The diced cartilage technique for the filling of defects under the skin is one of these. Yet there is a need for further versatility in the adoption of useful implantation materials.

Prosthetic implants of ivory, celluloid, steel and tantalum are a partial fulfillment of the need for such materials. The newer synthetic resins, those which can be polymerized to a state of biologic inertness, promise immense advantages in this field.

As the public becomes accustomed to what is being done in the way of prostheses for the face, requests have come for restorations hitherto considered not only beyond the scope of plastic surgery, but also beyond the scope of prosthetics. One's first impulse is to tell such a patient that the restoration asked for is not being done. But the plastic surgeon who does prosthetic work must realize that his office or clinic is the court of last resort for such patients and, if he had no restoration to offer, the patient may become convinced that his case is hopeless. He is besieged by requests not only to restore missing parts of the face, but also to restore other parts such as the breasts, the hand, the buttocks, the penis and the calf of the leg.

Small prostheses for the face can be made of solid rubber or hollow rubber, molded by relatively simple techniques. Prostheses for the breast, the buttocks and the calf of the leg, if made by the same technique, would be heavy, bulky, unwieldly and relatively non-resilient. They should be light enough in weight so that a relatively small amount of adhesive will keep them in place, or so that no adhesive at all is necessary. They should also, unlike facial prostheses, have the rebound elasticity characteristic of the organ which they replace. For instance, when the artificial ear is bent forward and released, it should spring back into place immediately, as does an ordinary ear. Likewise, the artificial calf of the leg when pressed with the finger, should rebound at the rate normal for calf tissues.

There is no doubt that the atomic age and bacteriologic warfare will bring new and maliciously clever methods of destruction to light in our generation. This is to be normally expected. World War II produced many more facial and body mutilations than resulted from the First World War. With the next struggle, civilian populations will be even more intimately involved, and, as at Hiroshima, many thousands will suddenly be left hideously deformed.

Plastic surgical procedures designed to correct disfigurations have more or less kept pace, limping forward, as the needs of each new problem were evident, to develop new plastic surgical techniques to meet them. Even today it has been found inadvisable to operate on all mutilating injuries. Frequently it is better to replace missing parts of the face and body with lifelike substitutes than to attempt reconstruction with living tissue. Some of the reasons for declining to attempt surgical tissue alterations are intercurrent disease, the fragility and atrophy of the host tissue, and the natural debility of age. The new atomic and bacteriologic warfare will beyond doubt increase the first 2 categories of facial and body deformities which will be beyond the restorative power of plastic surgery. For the atrophy, the telangiectasis, the keloidal change and the precancerous condition of atom-bomb exposed tissue forbids surgical modelling. Nor can surgical sculpture be tolerated by tissues whose hematopoietic system is deranged.

All this will lead the medical profession to a more serious consideration of the prosthetic art. Prosthetic restoration techniques have until recently been an orphan child of the medical profession—one might almost say a bastard child of medicine. Restorative cases were grudgingly admired for the moment, but given neither permanent nor recognized places in the clinics or medical schools. And cases beyond the power of plastic surgery have only grudgingly in the past been assigned for prosthetic correction. It seems that only by the "bloody" correction could a patient be really benefited according to most members of the healing profession.

Despite the almost "do-nothing" attitude of medicine as a whole, some men have tried through the ages to replace missing parts of the face and body with substitutes, rather than attempt reconstruction with living tissue.

Some of the substitute materials, notably latex rubber[2] and some of the newer polymerized synthetic resins, such as polyvinyl butyral, have already proven their worth as restorative substances. The surgeon is the first to confess that reconstructive operations, such as that of the total ear, often at best carry the probability that the esthetic result of a whole operative series will be only fair. By prosthetic techniques, though, an ear of latex or of vinyl resin can be made to match its mate with accuracy, both as to color and translucence, with lifelike elasticity, and certainly with excellent sculptural details. Such an ear, applied with a perspiration resistant cement, can be produced without pain, without hospitalization or loss of the patient's working time. It is easier on the patient, the doctor and Society. After a few recent wars,

with the subsidization by government, rehabilitation with prostheses among both military and civilian population is an improved and broadened art. Using the most suitable of the new synthetic compounds as fast as they are developed, the modern prosthetic expert is keeping pace with advancements in industrial fields.

All this is being accomplished by a few medical men who form an inner clique of men interested in helping the cases heretofore considered beyond ordinary help. Men unconsciously dedicating themselves to help the poor patients who heretofore were transferred from department to department, from clinic to clinic, with nothing offered, to conceal if not correct, their revolting faces, and make life more endurable.

To help such people, however, requires more than the ordinary knowledge held by possessors of an M.D. degree. Men who seek to restore these deformities must have some knowledge of art, whether it be formally acquired or not. They must have mechanical ingenuity; they must have a practical ability in chemistry —they must be improvisers, experimenters, and true practitioners of medical art. They must have obstinancy and courage—courage enough to carry through and produce previously impossible-to-make artistic restorations, courage to overcome the obstacles intrinsic to each unusual case as it presents itself, and above all, courage enough for the patient, too.

Fortunately, there are such men in medicine. It is a credit to our profession that there are men willing to undertake this unprofitable (yes, unprofitable), exciting, and often exasperating work. Because of these true physicians, new names are creeping into medicine. Insinuatiug into medical terminology are the names of vinyl resins, synthetic latices, neoprene dispersions, the methacrylates, new monomers and plasticizing agents.

New products of manufacture now rest in the doctor's laboratory. Colored lacquers, tints and dyes from all industry are now combined to make artificial restorations the important adjuncts of surgical—and medical—practice they deserve to be. And the patient with inoperable lupus of the face, the patient with hideous tertiary syphilis, even unresponsive to medication, is helped.

Special equipment is now visible in the doctor's laboratory. Heaters, ovens, mixing equipment, homogenizers, grinders, polishers, calking guns, are borrowed from industry to help the deformed. This is as it should be.

There are definite satisfactions which come to one who undertakes this sometimes heart-breaking work. Among them is the comradeship which develops between men of various professions for a common cause. Once the purpose of the work is explained, the coöperation from engineers, chemists and other researchers in industry is astonishing.

But there are other satisfactions. They might be called secret satisfactions. All doctors find time to think of their work at odd moments, when they are driving, smoking, drinking coffee with friends. They think of their work, naturally; of provoking cases, of puzzling reactions. What does the doctor think of who has found himself captivated by the restorative art? What are some of his basic problems? He finds that present problems are linked to the latest discoveries of industrial chemistry, and finds fascination in attempting to adapt these newer techniques to his own art for the benefit of his patients. He finds that his art is retrogressively connected with the art problems of the Renaissance. He cannot reconstruct artistically without a knowledge of the rules of proportion. For these he cannot depend, strangely enough, on modern textbooks; he must go back and examine the observations of Leonardo da Vinci on anatomy, and for the laws of optics as they apply to shadow, to Albrecht Dürer for some rules of facial harmony. He must investigate Brunelleschi and Botticelli, who, with Dürer and Leonardo, helped to develop an artistic naturalism. It is clear that today the medical restora-

tive artists are a small circle of kindred spirits, more interested in things than in idle hypothesizing, and more interested in experimental inquiry than in hackneyed medical and surgical opinion.

The modern practitioner of restorative art finds himself wondering upon the nature of color. He finds himself reading the theories of color, practically and philosophically. The theories of color of Des Cartes, of Hooke, of Bacon, become important. In the time of Newton, Grinaldi showed that very narrow beams of light, ordinarily travelling in straight lines (page Einstein!) are bent at the sharp edges of obstacles, so that the shadows are larger than they really should be, and fringes of color are formed. Newton showed that the bending is increased by passing the light through a narrow slit. All these behaviors of light, of shadow, of color, occupy the attention of the modern restorative artist. Thus, ultra-modern as is his work, he is united in spirit with the artists and scientists of all ages.

He finds himself posing questions which are strange to modern medicine. Why are fingernails, the cornea and tooth porcelain fluorescent to ultraviolet light? If artificial teeth, artificial eyes and artificial fingernails possess fluorescence by artificially adding coal-tar extracts to them, why are they more lifelike? Why is blue sometimes discernible in Negro skin? How much of skin color is due to pigment, how much to transmitted color from the flesh below? How fluorescent is sebum? Is perspiration fluorescent? What is the mechanism of scoliosis after breast amputation?

These are the questions posed to modern practitioners of the restorative art. These problems, to the average doctor, seem annoying. To those who do this work, these problems are exasperating—but delightful.

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BOOK REVIEWS AND NOTICES

MEDICAL ADDENDA. RELATED ESSAYS ON MEDICINE AND THE CHANGING ORDER. By NEW YORK ACADEMY OF MEDICINE COMMITTEE. Pp. 156. New York: Commonwealth Fund, 1947. Price, $1.75

THESE essays constitute a more complete exposition of the modern trends in the practice of medicine as visualized by the Committee on Medicine and the Changing Order of the New York Academy of Medicine. The names of the contributors, J. A. Miller, L. Hamman, Mary A. Cannon, Winifred W. Arrington, H. A. Rusk and E. P. Boas, indicate the high quality of the material presented. The book should be on the desk of everyone interested in medical practice.

T. M.

THE SKIN MANIFESTATIONS OF INTERNAL DISORDERS (DERMADROMES). By KURT WIENER, M.D., Dermatologist, Mt. Sinai, Deaconess, and St. Michael's Hosps., Milwaukee. Pp. 690; 400 ills.; 6 color plates. St. Louis: C. V. Mosby, 1947. Price, $12.50.

THIS is a satisfactory book which fills a long-felt need for the general practitioner, the internist and the dermatologist. It should go far to dispel the "superficial" nature of dermatology and to place this branch of medicine in its proper position as an integrated part of a whole.

While there have been previous attempts to compile the dermatologic aspects of internal diseases, the efforts have been somewhat sketchy and incomplete, and are now out-of-date. Here the author has produced in a reasonably-sized volume a comprehensive, fairly complete, discussion of "dermadromes"—a word the author coined to represent the cutaneous part of a syndrome. The material is presented in sufficient detail, as a rule, to be adequate for the particular medical public for whom the volume is intended.

A wide range of subjects is covered. In 43 chapters, are considered: the Dermadromes of Systemic Infections; of Helminthic Diseases; of Tuberculosis; Dermatoses with Claimed but Still Controversial Tuberculous Etiology; Leprosy; Dermadromes of Intoxications; of Disorders of the Circulation; Kidneys; Endocrine Glands; including also Puberty, Menstruation; Pregnancy; Childbirth and the Puerperium; the Skin of the Newborn; Menopause, and Miscellaneous Dermatoses with Endocrine Background; Ageing; Metabolic Disorders; Disorders of the Blood and Blood Forming Organs; Internal Cancer; Disorders of the Nervous System; Gastrointestinal Tract; Liver and Pancreas, and Respiratory Tract.

The material is well illustrated by clinical photographs from a variety of sources (no one man's personal experience could encompass all the data presented). Bibliographic references are given as footnotes on the same page as the material to which they refer, a method Wiener prefers not only as a matter of fairness to the author quoted, but also to induce the reader to look up some of the original sources himself. This is apparently becoming good American procedure in medical book publication, one of which the reviewer approves.

The reader will understand that the criticisms which follow are intended to be illustrative and not to detract materially from the value of the book as a whole. While its general format is excellent, color-plates, costly and superficially attractive, are in a state of technical development which seldom justifies their wide use instead of black and white illustrations. When added to this a number of unrelated color-pictures are put on one plate, somewhat removed from the text, they become like so much wall paper—this is the situation in Wiener's book. There are few typographical errors. A generally better correlation of plates and pictures with the text, more widely used terminology, as well as uniformity of spelling, would strengthen future editions. At first glance, the reviewer is struck by the numerous citations of foreign (viz. German) references (a reflection of the author's medical background) but a more critical study of the text reveals that very little in the American literature is omitted. The only fair conclusion is that the author is admirably suited

to his task because his training and experience have given him a grasp of the American, as well as European thought.

The use of eponyms is over done. The index is far from complete. Since the quality of the index makes or mars the usefulness of a book intended chiefly for reference, this is especially unfortunate. It is possible to make up an arbitrary list of subjects which are covered in the text but cannot be found in the index.

Moreover, an excellent feature, placed at the end of the book, is the group of tables on the Acute Exanthems; Diffuse Pigmentations; Diffuse Yellow Pigmentations; Hirsutism; The Skin in Relation to Age; The Hemorrhagic Diseases and Pruritus. They serve as ready reference and it is hoped that many more of them will be added in future editions.

The omission of a presentation of Syphilis is regretted. At least a photographic representation of the cutaneous aspects of Syphilis, and some differential tables would be helpful.

Allergy is becoming more and more important in certain aspects of dermatology, especially so in the case of food allergy. That there is no real presentation of allergy in such a book as this is a serious omission. Among some of the items which might be expanded are: Periarteritis Nodosa and its relationship to drug allergy (Sulfonamide); a discussion on "Stevens-Johnson's Syndrome;" Sporotrichosis as a systemic disease; Granuloma Inguinale as a systemic disease; a wider discussion of Telangiectasia; Symmetrical Erythema of the palms; more discussion of Panniculitis; more up-to-date Leprosy discussion; Premenstrual tension; Protein Metabolism, Water Balance, and Cutaneous Disorders.

The reviewer has tried to be as critical as possible; but aside from easily-corrected shortcomings, he has nothing but praise for a volume which fills the great need for better understanding between the Dermatologist and his colleagues. H. B.

THE ENGRAMMES OF PSYCHIATRY. By J. M. NIELSEN, M.D., F.A.C.P., Assoc. Clinical Prof. of Neurology and Psychiatry, Univ. of Southern California, and GEORGE N. THOMPSON, M.D., Formerly Chief of Psychiatric Service, Los Angeles County General Hosp. Pp. 509; 28 ills. Charles C. Thomas, 1947. Price, $6.75.

IN this 500 page description of the neural patterns of normal and abnormal thought the physician is told that he can "move in an orderly manner and accurately—in a psychiatry which is concrete and factual" and which is founded on the basic sciences of anatomy and physiology.

The authors have made an earnest, conscientous and interesting effort to find what neural patterns underly conation, instincts, will and the personality. The definitions are pretty much their own. A typical statement is that "psychosomatic" should be changed to "brain-somatic," as it is the brain and not the mind which sends messages to the soma.

The psychoneuroses are covered in 27 pages (psychopathic personality in 40). The psychoses are introduced by schizophrenia. In this illness the commonest upsesting factor is given as "infectious illness;" the pathophysiology depends on "engrammes located in the diencephalon" which are disorganized; the disease later spreads to the cortex; the symptomatology is to a considerable extent physical; the treatment is shock therapy followed by re-education. In the chapter on Treatment in Psychiatry, about half of the procedures are given as physical and half as psychotherapy.

The reader interested in psychoanalysis will turn to another book.

E. B.

MEDICAL DISORDERS OF THE LOCOMOTOR SYSTEM, INCLUDING THE RHEUMATIC DISEASES. By ERNEST FLETCHER, M.A., M.D., (Cantab.), M.R.C.P., of the Royal Free Hosp., etc. Pp. 625; 262 ills. Balt. and London: Williams & Wilkins, 1947. Price, $11.00.

IN this book, Dr. Fletcher and 9 contributors attempt "to bring under one cover the available information on the subject of the medical locomotor disorders." They exclude the cerebrospinal system.

Following a review of the anatomy of the joints, muscles and bones, 4 chapters describe rheumatic fever and chorea, 12 chapters deal exhaustively with the more common arthritides and 2 chapters contain brief descriptions of many of the rarer affections of the locomotor system. Among others, one notes

single chapters on examination of the patient, joint physiology, fibrositis, medical diseases of bone, focal infection, radiology, gout, sciatica, and physical therapy.

The material is sometimes more abundant than well organized; *e. g.*, under "Treatment of Rheumatoid Arthritis" a discussion of 10 drugs is followed by a page or so on "Exercises for the Arthritic Patient" which is, in turn, followed by a discussion of 7 more drugs. Reiter's Arthritis is inadequately described on page 287, and fully described on page 406, although the latter is not indexed. For some reason scleroderma, dermatomyositis and myasthenia gravis are dismissed in a few words but space is found for Paroxysmal Proctalgia, although it seems hard to identify the rectum as part of the locomotor system.

The book is well bound and illustrated. Its great mass of facts are valuable from the historic, scientific and clinical aspects of rheumatism. It will be particularly useful as a reference book to the internist who is already interested in rheumatism.

J. L.

HISTOPATHOLOGY OF THE EAR, NOSE AND THROAT. By ANDREW A. EGGSTON, B.S., M.D., Director of Laboratories, Manhattan Eye, Ear and Throat Hosp., and DOROTHY WOLFF, A.B., M.A., PH.D., Research Investigator Endaural Hosp., New York. Pp. 1080; 505 ills; 28 color plates. Balt.: Williams & Wilkins, 1947. Price, $18.00.

ALTHOUGH the book will generally speaking be of great value both to the otorhinolaryngologist and the pathologist, its title is somewhat misleading. Histopathology as such is the weak point of the volume. The microscopic appearance of the various lesions described is covered rather briefly for a work of this size, and such descriptions as do appear tend to be poorly presented and buried under a wealth of other material.

The interest of the authors seems to center about anatomy, gross and microscopic, embryology, and physiology. A separate chapter is devoted to each of these subjects as it applies individually to ear, nose, and pharynx. These reviews are at once clear and comprehensive. Particularly good are the chapters on comparative anatomy in which the development of the respective organ is traced from its beginning in *Amphioxus* and the lower vertebrates.

Clinical correlation is foremost in the chapters devoted to pathology. Especially emphasized are gross pathology as seen by the clinician, routes of spread, in the case of infection and tumors, and prognosis. From this point of view the book is of equal or greater value to the clinician than to the specialist in pathology. Of special value to the pathologist are several sections on the technique of dissection of the regions discussed.

The volume is greatly enhanced by extensive references at the end of every chapter, and by excellent and numerous illustrations; photographs, line drawings and color plates. The historical background of many diseases is presented in great detail.

A. R.

CINEPLASTY. By HENRY H. KESSLER, M.D., PH.D., Foreword by ROSS T. MCINTIRE, Vice-Admiral (M.C.), U.S.N. Pp. 210; 314 ills. Springfield, Ill.: Charles C Thomas, 1947. Price, $6.75.

THIS book is written by the one in this country who has probably had the most experience and interest in rehabilitation surgery. The intricacies of cineplasty are not too well known even by the best of orthopedic surgeons and Dr. Kessler stands out as the one willing to devote his time and effort to this branch of rehabilitation. He reviews the mechanics of the hands and details the various types of mechanical prostheses and discusses their advantages and disadvantages. The physiology and anatomy of the muscles of the upper extremities are discussed with respect to their function as motors. His chapter on Surgical Technique discusses the possibility of forming useful motors from remaining muscles. The various procedures are described in detail, both for below-the-elbow amputations and for those above the elbow. Cineplastic prostheses are described and illustrated. Finally, considerable emphasis is placed upon the rehabilitation of the amputee in helping him to regain his self-confidence and to return to a useful life. Dr. Kessler's book is of particular value to those interested in rehabilitation as well as to orthopedic surgeons. It is probable such cases will be referred by those who have read this book to men who have had experi-

ence in this type of work. The impression gained by the reader is that this is not a type of surgery to be attempted by the inexperienced.

The illustrations, taken from Dr. Kessler's own cases, are excellent.

L. F.

THE MEDICAL WRITINGS OF ANONYMOUS LONDINENSIS. By W. H. S. JONES, LITT. D., F. B. A. Pp. 163. Cambridge, at the University Press. New York: The Macmillan Company, 1947. Price, $2.75.

THIS is the first English translation and critical edition of a British Museum pagyrus (dating probably from the second century A. D.) that was discovered in 1891, and the *editio princeps* o which was brought out in Germany in 1893. A German translation was published in 1896.

The papyrus is a copy made by a medical student, W. H. S. Jones conjectures, of lecture notes also made by a medical student, perhaps on several lectures. The work falls into three distinct parts: (1) definitions; (2) descriptions of the views on pathology of predecessors and contemporaries of Hippocrates; (3) a history of physiology after 300 B C. from Herophilus to Alexander Philalethes. The second part is of particular importance as representing more fully than hitherto the non-extant historical work of the Greek physician Menon, a pupil of Aristotle. Indeed, the passage therein describing the views of Hippocrates is coming to be accepted as one of only two reliable testimonies for the doctrine of the historical Hippocrates.

Text and translation are printed on facing pages. An introduction records the critical history of the text since 1893, describes the contents, and discusses the problems of authorship and sources. Additional notes, footnotes, a bibliography, and an index of *notabilia* complete the scholar's apparatus. An excursus, there are a note on the nature of Greek thought and another on the nature of Greek Medicine.

It is good to have this important text made available in English by a scholar so singularly well-equipped to elucidate its complex fabric and meaning.

W. McD.

OSTEOTOMY OF THE LONG BONES. By HENRY MILCH, M.D., Consulting Orthopedist, Maimonides Hospital. Pp. 294; 181 ills. Springfield, Ill.: Charles C Thomas, 1947. Price, $6.75.

AN accepted method of effecting an osteotomy of a long bone 25 years ago was by a thrust of a chisel through the skin to the underlying bone, a twist of the handle to bring the blade transverse to axis of the bone and a whack by a mallet to produce the dissolution of the bone. The alignment of the fragments was judged mainly be external appearances. The duration of immobilization for union of the osteotomy was by "rule of thumb." With the coördination of the knowledge of pathology, physiology of bone, roentgen study and improved surgical technique, the method of effecting an osteotomy has become more complex; but a greater range of application has been attained and a uniformity of better results.

Dr. Milch has written a book which correlates the many advances in the analysis of deformities of the long bones and their mechanical correction. He frequently reveals the advantage of using a mathematical equation to obtain the desired mechanical result. His abduction osteometer is an ingenious apparatus for determining the optimum angle of correction for hip joint deformity. In a logical manner he considers the 4 directions in which displacement may occur when an osteotomied long bone deviates from its mechanical axis. He considers 4 types of osteotomy that produce a monoaxial displacement in each of the 4 directions: (1) lineal, with displacement longitudinally for shortening or lengthening; (2) torsional, for correction of rotation deformities; (3) transpositional, with displacement laterally so that the axis remains parallel to the original axis; (4) angulated, with the distal fragment angulated about any point along the axis.

This book sticks to the subject. It is a manual on the mechanics of osteotomy of the long bones. It does not deviate into diagnosis or operative technique. It is an excellent source book for the orthopædic surgeon.

J. N.

NEUROPATHOLOGY, ITS CLINICOPATHOLOGIC ASPECTS. By I. MARK SCHEINKER, M.D. Foreword by TRACY J. PUTNAM, M.D. Pp. 306; 208 ills. Springfield, Ill.: Charles C Thomas, 1947. Price, $6.75.

THIS book is highly recommended as valuable both to the neurologist and the path-

ologist. Although the volume is brief, the included subjects are discussed fully and to the point. The style achieves easy reading and the subject matter is clearly and concisely presented. The chapters are well arranged, in logical sequence. The principal topics discussed are vascular diseases, demyelating diseases, neurosyphilis, inflammatory diseases, myopathies, syringomyelia, cerebellar disorders, and degenerative diseases. Conspicuously absent are such important topics as tumors, congenital malformations, and intoxications; and this, in the opinion of the reviewer, is the principal adverse criticism of the book.

Concise historical reviews are given for each disease. The pathologist will appreciate the lucid descriptions of both gross and microscopic findings. The clear and well-chosen illustrations are helpful in supplementing the verbal descriptions. The clinician will be interested in the excellent clinical descriptions of the included diseases, and in the close clinicopathological correlation. The bizarre terms that clutter many works on neuropathology have been largely replaced by those more familiar to the average physician. An unusually good presentation of the various encephalitides, and of fungus diseases of the central nervous system is included. An extensive bibliography is provided. A. R.

DIAGNOSTIC BACTERIOLOGY. By ISABELLE GILBERT SCHAUB, A.B., Instructor in Bacteriology, Johns Hopkins Univ., and M. KATHLEEN FOLEY, A.B., Instructor in Bacteriology, College of Notre Dame of Maryland. 3d ed. Pp. 532. St. Louis: C. V. Mosby, 1947. Price, $4.50.

THIS is a technique book of determinative bacteriology, divided into 3 principal sections: (1) Bacteriological Diagnosis, (2) Serological Diagnosis, and (3) Media, Stains and Staining Technique, etc. As in previous editions, methods for the isolation and identification of bacteria are given clearly and concisely step by step and day by day. Included with each group of organisms are numerous tables showing the differential procedures to be followed. In this edition there are new tables for the intestinal Gram-negative bacilli and the aerobic streptococci. A new Chapter 1 concerned with elements of technique has been added. This edition has been expanded also to include explanatory and theoretical discussions of technique. The left-hand pages again are blank for student's notes.

As is the case with most technique books concerned with such an inexact science as diagnostic bacteriology, the methods recommended will not be approved by all. The authors have had wide experience in the isolation and identification of pathogenic bacteria, however, and the techniques in general are sound and practical. Consequently the book should be especially useful for technicians and medical students and should be a valuable addition to any library of clinical bacteriology. R. N.

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